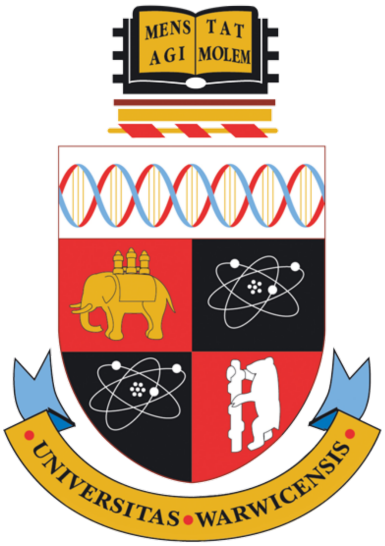

Adaptive management of infectious disease epidemics

by

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Contents

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Declarations

The work presented here is my own, except where stated otherwise. This thesis has been composed by myself and has not been submitted for any other degree or professional qualification.

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Abstract

Infectious disease epidemics present a difficult task for policymakers, requiring the implementation of control strategies under significant time constraints and uncertainty. Mathematical models can be used to predict the outcome of control interventions, providing useful information to policymakers in the event of such an epidemic. However, these models suffer in the early stages of an outbreak from a lack of accurate, relevant information regarding the dynamics of spread and the efficacy of control. As such, recommendations provided by these models are often incorporated in an *ad hoc* fashion, as and when more reliable information becomes available.

We propose and motivate the use of adaptive management (AM) as a solution to this problem. AM is an iterative, structured decision making framework, encouraging the incorporation of real-time information, resolution of uncertainty and adaptation of control as an outbreak progresses. We investigate in detail how the AM framework can be applied to the management of epidemics. We clarify the effects, benefits and limitations of certain components, such as the difference between active and passive optimisation and the method used to predict uncertainty resolution. We cover a range of scenarios, exhibiting the value of an AM approach in guiding decisions under uncertainty and providing relevant, clear information to decision makers regarding efficient allocation of control and monitoring resources. We believe the practical implementation of such an approach could greatly improve the outcome of epidemics in the future.

Chapter 1

Introduction

The management of infectious disease epidemics is a task beset by difficulties. It requires satisfying the complex, often conflicting, objectives of stakeholders, without complete knowledge of how the disease will spread or the effect that control interventions may have. Mathematical models have become a useful tool to aid in the decision making process, allowing the comparison of different strategies through simulation. Since their advent in the influential work of Kermack and McKendrick [1], mathematical models describing the spread of diseases through time and space have become both increasingly commonplace and complex. The vast improvements in both theoretical and computational techniques that have been achieved and utilised in this field allow for models that can accurately represent and mimic what we see in real-world systems and predict future outcomes.

However, whilst mathematical models are now well established in epidemiological contexts [2, 3], incomplete knowledge of the system under question remains a significant barrier to providing relevant policy recommendations during an epidemic [4–7]. In the context of a novel outbreak, control strategies must be decided upon and implemented quickly, leaving little time to gather accurate information about the current outbreak, such as the transmissibility of the disease or the efficacy of a vaccine. In the past, retrospective analyses of historic outbreaks have often been used to estimate such parameters. Although such estimates are often accurate for the outbreak on which they are based, there is no guarantee they will be the same for another outbreak, even if it is the same disease and other conditions are comparable. Furthermore, in such instances, real-time information has often been ignored or used in an *ad hoc* fashion as the outbreak progresses, resulting in heavy reliance on possibly inaccurate historical data. There is a growing body of literature highlighting the significant effect that uncertainty can have on the outcome of control policies and, as

a result, the selection of optimal control (e.g. [8–11]). Such results demonstrate the need for formal uncertainty estimation and inclusion in epidemiological forecasting and decision making.

Real-time parameter estimation and epidemic forecasting has become a significant area of focus in recent decades, with several large outbreaks catching the attention of both the epidemiological community and general public. The 2001 Foot-and-Mouth disease (FMD) outbreak in the UK [8, 12, 13] has since prompted significant research into the process of real-time decision making and forecasting that continues to develop [10, 14–17]. Soon after, outbreaks of severe acute respiratory syndrome (SARS) in 2003 [18], pandemic H5N1 influenza in birds from 2005 [19] and a novel H1N1 human influenza pandemic in 2009 [20] led to increased preparation for similar outbreaks in the future through methods of estimating and forecasting disease potential [21–26] and analysis of control and surveillance options [27, 28]. The role of dynamic policies that can adapt to the real-time characteristics of such an outbreak has also seen increased attention in this area [29–31].

In 2014, West Africa suffered an unprecedented Ebola epidemic [32], triggering an impressive response from epidemiologists in estimating transmissibility, forecasting burden and patterns of spread, predicting the efficacy of interventions and assessing the possibility of vaccine trials (e.g. [33–35], see [32] for an extensive list). Forecasts from such models aided in advocating for important international public health response [36], crucial to the early control effort. Since then it has resulted in initiatives such as the RAPIDD Ebola forecasting challenge [37], providing insights into modelling methods as well as better practices for future outbreaks such as greater collaboration between groups and the need for quality data [32, 36].

At the time of writing this thesis, much of the world is enforcing strict social distancing measures in response to the ongoing novel coronavirus (COVID-19) pandemic [38–40], which has currently been detected in over 3 million people worldwide [41]. Epidemiological modellers have been providing significant support to the UK government during this response, through the Scientific Pandemic Influenza Group on Modelling (SPI-M), providing real-time estimates of the epidemic potential, forecasts and predictions regarding interventions.

Overall, it is clear that the methods and analysis provided by mathematical modelling and the wider epidemiological community serve as a vital tool for decision makers to help with understanding the current state of the epidemic, the impact of possible control interventions and the uncertainty surrounding both. However, the formal integration of such information into management decisions in real-time

remains a significant difficulty [5, 6], both due to a disconnect between modellers and decision makers and because modelling results can be highly uncertain, appearing to change rapidly and unpredictably to untrained eyes.

We propose the adaptive management (AM) framework as a way to tackle this problem, by providing a rigorous structure for estimating epidemiological parameters and adapting control. AM is an iterative, structured approach to decision making that provides dynamic, state-dependent decision recommendations, encouraging the incorporation of real-time outbreak information to resolve uncertainty in system parameters where necessary [42]. It is well-established in ecological fields, such as conservation and resource management [43, 44], and has recently gained attention in the literature surrounding epidemiological interventions (e.g. [11]). However, widespread, interdisciplinary use has been hindered by a lack of consensus on the definition of AM and a lack of understanding as to how AM differs from current methods of management, such as *ad hoc*, trial-and-error type approaches. In this thesis, we introduce AM in a epidemiological setting, clarify how it differs to current management approaches and exhibit several ways in which it can help to improve the outcome of management during an epidemic.

In Chapter 2, we start by introducing many of the important methods and ideas that we will use throughout the thesis. These include a formal definition of the AM framework and a review of its use in the literature, an overview of Value of Information analysis and its use in conjunction with AM and an explanation of the parameter inference techniques and software used throughout.

In Chapter 3, we begin our analysis of the AM framework and its use in the management of epidemics. We introduce and compare three approaches to managing a theoretical epidemic: a non-AM, passive AM and active AM approach, contrasted by how they incorporate real-time information into decisions and plan to resolve uncertainty in the system. Using vaccination as the only form of control, with an unknown vaccine efficacy, we focus on how these approaches can lead to different initial control decisions and thus affect the outcome of the epidemic. We find that using an active AM approach to management enables us to better satisfy management objectives compared to using other, less complex approaches, as well as provide relevant, useful information to decision makers that is not possible under other approaches.

In Chapter 4, we focus on the use of active AM to optimise the timing and allocation of resources for both control and monitoring, in the face of uncertain epidemiological parameters such as the transmission rate. We introduce three

methods of modelling uncertainty resolution: a 'perfect information' method, an abstract method that does not depend on the state of the outbreak itself and a fully mechanistic method that attempts to model the mechanism behind uncertainty resolution exactly. We again focus on the initial decision and how these different methods can change early recommendations regarding control and monitoring, such as the timing of cross-sectional samples of the population or the targeting of one uncertainty over another. When testing the performance of these methods on a theoretical epidemic, we find that active AM, coupled with a mechanistic model of uncertainty resolution, is able to provide the most accurate and relevant information to decision makers, emphasising the need for a clearly defined monitoring plan before the implementation of control.

In the final two chapters, we show how the techniques we have developed in Chapters 3 and 4 can be used in a more realistic setting to provide important information to decision makers and help to improve epidemic outcomes. We focus on an Ebola-like disease model, introduced in Chapter 5, with both vaccination and the establishment of healthcare centres as possible forms of control. In Chapter 5, we show how an increase in 'risky' behaviour from vaccinated individuals can lead to an increased number of deaths from a mass vaccination campaign if vaccine efficacy is low. Hence, if vaccine efficacy is unknown, it is beneficial to gather information regarding vaccine efficacy before implementing a mass vaccination campaign. We assume that this information is gathered through a vaccine trial. We show how active AM, coupled with a model used to simulate the vaccine trial, can be used to provide time-dependent thresholds for the estimate of efficacy needed to ensure that vaccination will improve the outcome of the epidemic. Finally, we incorporate an unknown transmission rate and use active AM to develop time- and state-dependent thresholds for the implementation of a mass vaccination campaign, dependent on both the estimate of vaccine efficacy obtained from a trial and the probability distribution of the transmission rate estimated from the state of the epidemic over time. We demonstrate how the two uncertainties can interact with each other and the importance of capturing such effects within the model.

Finally, in Chapter 6, we use interventions targeted towards the healthcare-seeking behaviour of the population to control the outbreak, in the same Ebola-like disease model used in Chapter 5. We demonstrate that an increased probability of seeking healthcare can lead to significantly improved outcomes. However, it can also increase the burden on the healthcare system, an issue if it results in overloading the healthcare system. We show that a multi-phase AM procedure, with the choice to implement different levels of control during each phase, can improve

outcomes compared to a static control policy. We also show how an active AM perspective, anticipating the resolution of uncertainty at some point in the future, can change initial recommendations, greatly improve outcomes and provide important information to decision makers regarding the cost of delaying information gain (or, conversely, the benefit of making it a priority) and which uncertainties are most important to resolve.

Overall, in this thesis we present a significant body of evidence supporting the use of the AM framework, especially active AM, to aid in the management of epidemics. We show that the existence of uncertainty in both epidemiological parameters and the effects of control interventions can lead to unexpected and undesirable outcomes from control. However, using the rigorous, structured approach of AM, alongside an explicit, active treatment of uncertainty and its resolution, allows for clear, state-dependent control and monitoring recommendations that can help to significantly improve management outcomes through better decisions and allocation of resources. Such results have not been demonstrated before in the literature surrounding epidemiological interventions. We hope this work serves as a proof of concept and encourages further theoretical and practical exploration of the use of AM in this context.

Chapter 2

Background

2.1 Adaptive management

Adaptive management (AM) is a rigorous, structured approach to decision making that encourages iterative phases of learning and adaptation of control to better meet the objectives of management. First used implicitly by Beverton and Holt in 1957 [45] to improve the management of fisheries, adaptive management as an explicit methodology was introduced in 1978 by Holling [44] in the area of environmental resource management and soon thereafter applied by Hilborn and Walters [46] to harvesting policies. Since then, it has been subject to significant threoretical discussion, lead by Walters [43], often heralded as the best approach for managing ecological systems under uncertainty [47]. AM has seen several applications in real life [47, 48], for example in the planning of controlled floods along the Colorado River [49], or elucidating the relationship between harvest and survival rates in waterfowl populations [50] (we expand on these applications further at the end of this section). However, it has never been utilised for epidemiological interventions, only recently gaining attention in the literature [11, 51]. Here, we detail the structure and implementation of the AM framework in an epidemiological setting.

AM consists of two phases (Figure 2.1): a set-up phase and an iterative learning and implementation phase [42, 47, 48, 52]. Within the set-up phase, AM ensures the explicit specification of quantifiable objectives, possible management and monitoring actions and a model which accurately represents the behaviour of the system. These components must be decided upon *a priori*, with significant input from stakeholders. The set-up phase reflects ideas taken from structured decision making (SDM) methodology [52–54]. During the iterative learning and implementation phase, the set-up

components are used to forecast the possible effects of control and the action which best satisfies management objectives is implemented. As the outbreak progresses, it is monitored according to the agreed plan, providing information regarding uncertain parameters within the model. This real-time information is used to resolve uncertainty, allowing for updated forecasts of control outcomes and adaptation where necessary. The learning and implementation phase can be repeated many times throughout the outbreak. It is this explicit structure and objective-driven optimisation that sets AM apart from trial-and-error type approaches [55]. We reiterate and detail the individual components of the AM framework below and in Figure 2.1 (in depth reviews of the AM framework found in [42, 47, 52, 54]).

2.1.1 Components of the AM framework

Management objectives

In order to decide upon the 'best' control action in the event of an epidemic, it is necessary to agree upon the objective we wish to satisfy through management. Examples include: minimising the duration of the epidemic, loss of life, economic cost, or, more realistically, a combination of such factors. It is necessary that policy makers, in cooperation with stakeholders, explicitly state these goals *a priori*, in a quantifiable manner.

Control options

This component comprises a list of possible control actions that can be implemented throughout the outbreak. These must also be decided upon by policy makers in cooperation with stakeholders. We will use the AM framework to forecast and evaluate the outcome of these controls, in different combinations throughout the outbreak, to provide a structured, iterative control recommendation.

Monitoring plan

As the epidemic progresses, it is possible to gather information about its behaviour from a number of sources, for example the number daily infections or deaths or serological data describing the disease, as well as the effect of control interventions, for example the efficacy of vaccines. This component is essential for resolving uncertainty in the system and improving control. It is necessary to decide on what information to collect before choosing a control action, as this may restrict resources available

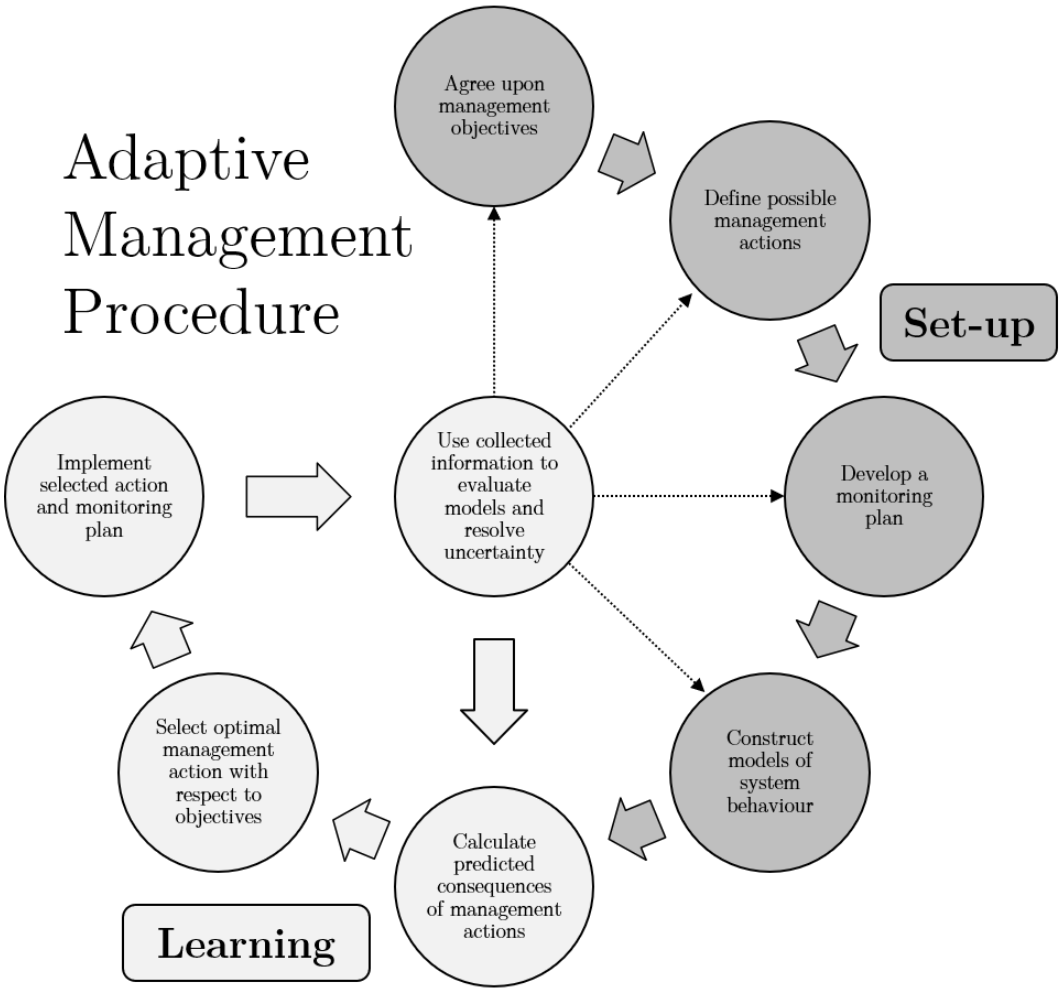


Figure 2.1: **Adaptive management procedure.** Adaptive management (AM) addresses the difficulties of epidemic control through a structured, iterative framework. The set-up phase (dark grey circles) provides a quantitative representation of management objectives, possible actions, planned monitoring and system behaviour, decided upon *a priori* with input from stakeholders. In the learning and implementation phase, the set-up components are used to forecast the possible effects of control. This allows a dynamic policy recommendation, outlining the actions that will best satisfy the management objectives whilst predicting the possible effect of updated outbreak information on the efficacy of control. As the epidemic progresses, predictions from competing models of system behaviour are compared to incoming information, reducing uncertainty in the effect of control. The recommendations are adapted as necessary and the process repeats. Dotted, black arrows indicate that new information may lead to changes in the set-up components. However, this impedes the ability of AM to select optimal control actions and should be avoided if possible through significant planning and discussion before control implementation. Figure adapted from [42]

for control and can affect the utility of some actions. Elucidating the interactions between control and monitoring and highlighting the benefit of a clearly defined monitoring plan before the implementation of control is a significant focus of this thesis.

Models of system behaviour

To predict how the disease may spread and how control actions will interact with this spread, quantitative models of system behaviour must be developed. It is essential that the models capture the key uncertainties within the system (that is, those that affect the recommended course of action [10, 11, 56]), as well as represent what is known or agreed about the system as accurately as possible. Using the information gained through monitoring, the models are evaluated for credibility in order to resolve uncertainty. This component of the framework encompasses an impressive body of literature from the epidemiological community.

In much of the literature, uncertainty is captured through the definition of multiple discrete models (e.g. [57]), with a weight attached to each representing its likelihood of being the true model. In this thesis, we focus on the treatment of continuous uncertainties, which are often found in epidemiological models. As such, the 'models' of system behaviour are contained within a single model whose parameters can take on a continuum of values. The weights are then defined by a continuous probability distribution on the parameters, which may change over time in relation to new information obtained from monitoring.

Optimisation

We use the models of system behaviour to forecast the outcome of control actions, with a level of uncertainty. How these forecasts are used to choose the optimal control action depends on the specific optimisation methods used; for example passive or active, myopic or dynamic. These classifications are explained in detail in the next section.

Implementation and adaptation

Once an optimal control action has been chosen, it is implemented alongside the monitoring plan. Real-time information gained from monitoring during the outbreak is then used to evaluate competing models of system behaviour, adjusting the weights

assigned to each model or, in the case of continuous uncertainties, the underlying probability distributions of model parameters. This allows control actions to be reassessed and adapted if necessary. In some cases (specifically active AM, defined in the next section), the effect of new information is anticipated before the initial implementation of control and monitoring, thus control can be adapted immediately according to new information without requiring optimisation to be repeated.

In light of new information, it is possible that components from the set-up phase need to be changed, for example new control or monitoring options may become available, or we gain a better understanding of the mechanics of spread. However, such changes, if not planned for, will detract from the ability of AM to identify the optimal course of action. This can lead to suboptimal and inefficient management, requiring repeating the process of optimisation as new information becomes available. Therefore, it is important that the set-up components account for as many such eventualities as possible, before the process of control optimisation, implementation and adaptation is started.

2.1.2 Optimisation methods

There are several methods for optimising the outcome of control actions within the AM framework. Here, we clarify the difference between some of the major classifications and indicate the definitions we will use throughout this thesis.

Passive vs active

Possibly the most important distinction between different optimisation methods within AM is that of 'passive' and 'active' adaptive strategies [57, 58].

Passive adaptive strategies represent a reactive method of adapting control, allowing adaptation of control if and when new information becomes available, but not anticipating future knowledge and the effect it could have on current decisions.

Active adaptive strategies explicitly account for the effect that new information gained in the future may have on current control decisions, by projecting future changes in uncertainty within the optimisation algorithms. This allows us to incorporate the effect that different control actions may have on future system uncertainty into current decisions. It also results in a multi-phase, state-dependent policy recommendation, allowing immediate adaptation of control in light of new information, without needing to recalculate optimal policies.

In Chapter 3 we go into significant detail regarding examples of passive and active AM and the difference between them, demonstrating how the anticipation of future learning can lead to different initial decisions when trying to control an epidemic. Thereafter, in this thesis we focus on the use of active AM and its utility.

Myopic vs dynamic

The choice of using myopic or dynamic optimisation is often dictated by the context [57]. Myopic optimisation focuses on the outcome one-step-ahead, choosing a control policy now that leads to the best outcome after one time step. This is useful for long-term management scenarios, often found in environmental and ecological contexts, for which the reward from an action is not immediately apparent or easy to define. In contrast, dynamic optimisation calculates the benefit of control actions across the entire time frame. Clearly, this requires a well-defined time frame across which to forecast the outcome of control, thus is better suited to short term management scenarios with clear goals.

In the context of epidemic control, dynamic optimisation is appropriate since we have clear goals, given by the management objectives outlined in the set-up phase, and a finite period of time over which to forecast the effect of control, that is, until the outbreak is suppressed. Employing an active, dynamic optimisation process also allows for learning to be prioritised, without explicitly attaching a reward to learning itself, since we are able to predict when learning in the short term will improve management in the long term. Throughout this thesis, we assume a dynamic optimisation strategy.

Favourite model vs utility averaged

Finally, given the uncertainty in the system, there will be a range of possible outcomes from each control action. Under a favourite model approach, we choose the control action which is best under the most likely model [57], or equivalently for a model with continuous parameter uncertainty, using the most likely values of parameters (the mode of the joint parameter distribution). Under a utility averaged approach, we choose the control action which is best on average (weighted), across all possible models or values of parameters. Given the importance of incorporating uncertainty in epidemic control, it would be unwise to use a favourite model approach, since it ignores this uncertainty. This could easily lead to unexpected non-linear effects when parameters differ from their most likely values. Thus, throughout this thesis, we use

utility averaged methods. In Chapter 5, we show how the objective of management may be further incorporated into this process, taking into account and limiting the probability of undesirable outcomes.

2.1.3 Implementation: methods, difficulties and successes

Markov decision processes

A common way to represent the adaptive management decision making process mathematically is using the theory of Markov decision processes (MDPs) [46, 51, 57, 59, 60]. MDPs are applied in contexts where we have a system that is observable over time and under the control of a decision maker [61, 62]. They are Markovian in nature, in the way that current decisions depend only on the current state of the system, not previous states or actions taken. A MDP consists of the following components:

Control phases: a set of control phases evolving through time t, determined by the decisions made between each phase. In epidemiological contexts, this set is made up of a finite number of discrete phases (finite-horizon, discrete time).

State space: the state space refers to the observable state of the system over time $\{s_t\}$. In an epidemiological context, the exact state of the sytem (the number of people in each compartment for example) is rarely observable. Instead, we use a proxy such as reported cases, which provides a probabilistic idea of the current state. This requires the use of partially observable markov decision processes (POMDPs), explained in the next section.

Actions: a set of actions $\{a\}$ that can be implemented during each control phase. The action taken will affect the state of the system.

Transition probabilities: a function that defines the transition of the system from one state, s_t, to another, s_{t+1}. The probability will depend on the current state of the system and the action that is implemented: $p(s_{t+1} \mid s_t, a)$.

Reward function: the immediate cost or value associated with implementing an action whilst in a specific state: $r(s_t, a)$. This can depend on the states and actions that are realised in the future, taking the form of an expected cost or value.

Finally, we define the overall accumulated value (or cost) of an action a over time (from now until the end of the decision process), assuming current state s_t, as $V_a(s_t)$. The goal of the MDP is to maximise the accumulated value (or minimise accumulated cost) through the selection of appropriate actions in each control phase.

Dynamic programming

Dynamic programming, developed by Bellman [61], is a common way to find the exact solution of a MDP. If the goal is to maximise the accumulated value $V_a(s_t)$, we proceed recursively calculating:

$$\max_a\{V_a(s_t)\} = \max_a \left\{ \sum_{s_{t+1}} p(s_{t+1} \mid s_t, a) \left(r(s_t, a) + \max_{a^*} \left\{ V_{a^*}(s_{t+1}) \right\} \right) \right\}, \quad (2.1)$$

where a represents the choice of current action to be taken and a^* future actions.

For a finite-horizon, discrete time MDP, this can be solved using backward recursion: start at the final time point and calculate the value $V_a(s_t)$ for all s_t and a. Then continue backwards, calculating $V_a(s_{t-1})$, repeating until we obtain the value function and corresponding optimal action for every possible state at each point in time. The choice of initial action will then depend on the initial state of the system, and subsequent actions in subsequent states. We present this process graphically in Figure 2.2, assuming a MDP with three time points, two possible actions at each step and a discrete state space.

Throughout this thesis we use a number of different objective functions, however, in general, we aim to minimise some 'cost' that is defined by the overall outcome of the epidemic and possibly the cost of implemented controls. As such, we will use minimising functions as opposed to maximising functions. Furthermore, the immediate reward $r(s_t, a)$ from an action will be the cost of implementing that action, plus, if it is the final decision point, the outcome of the epidemic that results.

Partially observable Markov decision processes

A limitation of the MDP definition we have described is the assumption that the state of the system s is observable. In the context of epidemiology, this is rarely the case. Instead, we rely on other observations such as reported cases as a proxy, providing a probabilistic view of what the current state may be. Such a scenario can be described as a partially observable Markov decision process (POMDP) [63–65].

To describe and solve a POMDP, we need to introduce a belief state, $b(s_t)$. This can represent a discrete set of weights for a set of models capturing the uncertainty in this system, or, as we use throughout this thesis, a continuous probability distribution over unknown model parameters. The belief state depends on the observed state s_t and changes over time. In the context of AM, we are aiming to resolve uncertainty

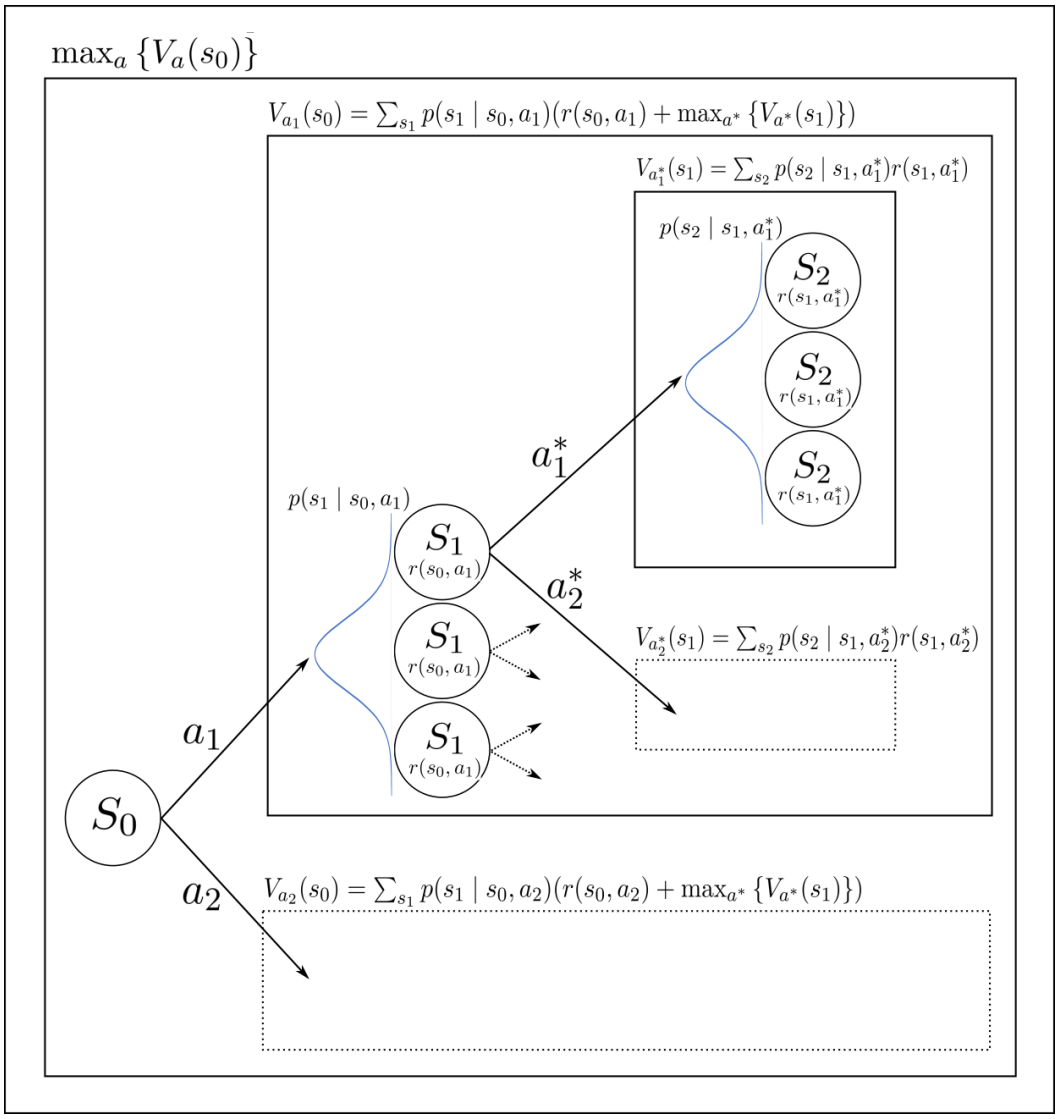


Figure 2.2: **Dynamic programming.** Dynamic programming is a recursive process used to find the optimal solution to a MDP. We present a graphical example of this process, described mathematically in Equation 2.1, for a MDP with three time points, $t = \{0, 1, 2\}$. The decision involves a choice between actions a_1 and a_2 at $t = 0$ and a_1^* and a_2^* at $t = 1$. The state space is represented by three discrete options. Each subsequent state is reached with a probability depending on the previous state and the action taken, $p(s_{t+1} \mid s_t, a)$. Each action and state pair results in a reward $r(s_t, a)$. The goal is to find the policy that maximises the accumulated value $V_a(s_0)$, subject to future decisions.

over time, thus we would expect the belief state to become more precise as time progresses.

The belief state gives us a new formulation for the accumulated value calculated in Equation 2.1. Assuming an active, dynamic, utility averaged approach [57], we aim to maximise the accumulated value $V_a(s_t, b(s_t))$:

$$\max_a\{V_a(s_t, b(s_t))\} = \max_a \int_\theta b(\theta \mid s_t) \sum_{s_{t+1}} p(s_{t+1} \mid s_t, a, \theta) \left(r(s_t, a, \theta) + \max_{a^*} \left\{V_{a^*}(s_{t+1}, b(s_{t+1}))\right\}\right) d\theta. \tag{2.2}$$

We can find the solution to this in a similar way to the MDP, using stochastic dynamic programming [61, 62], differentiated by the fact that the state and reward are not deterministic, but rather we must calculate an expectation. Again, for a finite-horizon, discrete time POMDP we can solve this using backwards recursion. The probability distribution representing the belief state is updated at each step using Bayes' theorem, with specific formulations introduced throughout when necessary. Finally, note that the active component of Equation 2.2 is incorporated in the $b(s_{t+1})$ term, representing that future value is calculated using updated belief states. For passive AM, this would instead be $b(s_t)$, as future value is calculated assuming that the belief state remains constant throughout. This difference is clarified in Chapter 3.

Barriers to implementation

Although AM has many proponents in the academic literature, there are a number of barriers that continue to hinder widespread adoption in practice. First, it suffers from a lack of clarity surrounding its definition and is often mistaken as equivalent to trial-and-error type approaches [42, 66–68]. The latter is easily refuted; the explicit structure of AM that requires the quantification of objectives and analysis of the effect of controls on system behaviour *before* any interventions are implemented immediately sets it apart from a trial-and-error approach [55]. However, there is still disagreement within the field as to the exact definition of AM. This, in part, arises from two schools of thought [48]: the resilience-experimentalist school and decision-theoretic school. The resilience-experimentalist school, rooted in the work of Gunderson et al. [69], focuses on the analysis of system resilience (the ability of a system to remain within its current state or return to an original state under perturbations) through experimentation, or active learning. This school often results

in highly complex models of system behaviour and requires significant input and understanding from stakeholders at all stages. The decision-theoretic school, with significant contributors including Possingham et al. [53] and Williams et al. [54], focuses more on the decision problem itself, requiring stakeholder involvement mainly for the formulation of objectives, relying on simpler models of system behaviour and theoretical exploration of the decision problem rather than experimental management. Both schools of thought encompass a significant body of supporting literature (resilience-experimentalist examples include: [70–76], decision-theoretic examples include: [54, 77–81]). Whilst they emphasise different components of the AM process, at their heart they boil down to the same idea: a structured, iterative process involving the concurrent implementation of control and monitoring that acknowledges and reduces uncertainty and drives the system towards a measurable objective.

In the context that we use AM throughout this thesis, we follow the decision-theoretic school of thought. There are two main reasons for this: first, it is often infeasible to have significant stakeholder involvement throughout the entire modelling process in the event of an epidemic. Rather, stakeholders are likely to only be involved in the definition of objectives. AM can then be used to provide decision makers with important information regarding the consequences of control, benefits of monitoring and possible adaptive interventions that can best meet the given objectives. Second, it may not be appropriate to rely explicitly on the concurrent experimentation of different control interventions to resolve uncertainty, given the moral issues that may arise, especially in a human disease context. Rather, we focus on how different sources of real-time information gathered during an outbreak may effect the timing and allocation of control resources. We show throughout this thesis that following an active AM approach is still hugely beneficial in this context. In Chapter 3, we give an example of how active AM can lead to different, more optimal, decisions compared to passive AM or non-AM approaches when experimentation of a single control is involved. In Chapter 4, we show that, even if experimentation is not explicitly involved in the resolution of uncertainty, the active anticipation of uncertainty resolution is still important, helping to more effectively time and allocate both control and monitoring resources. Both these ideas are supported and extended with further, more realistic, examples in Chapters 5 and 6.

Another barrier to the use of AM in practice is that it needs to be applied in the right context in order to see benefits from its use [42, 47, 66, 67]. That is, scenarios in which both controllability and uncertainty are high [42, 67]. Furthermore, we specifically require epistemic uncertainty, that within model parameters and the

effects of control which can be resolved, rather than aleatory uncertainty, the inherent randomness that exists in the sytem, which can not. There are multiple sources of epistemic uncertainty that need to be considered [42, 66], including partial observability (our ability to observe the state of the system), partial controllability (the unknown effect of control) and structural uncertainty (relating to the unknown dynamics of the system). Applying AM in inappropriate contexts detracts from the benefits obtained when used correctly. Throughout this thesis, we show that epidemiological interventions are an appropriate context in which to use AM, given the high level of uncertainty during early stages of the outbreak, availability of information collected throughout with which we can reduce uncertainty and the sensitivity of epidemic outcomes to the control interventions implemented.

Although a high level of uncertainty allows AM to excel over other methods, it also raises it own issues for implementation. Reducing such uncertainties requires significant support and commitment from the top down, in order to fund and facilitate the implementation of monitoring programs [47, 66, 77, 82]. In ecological contexts, such programs can be of significant, possibly indefinite, length. This makes them vulnerable to funding cuts and changes in policy or objective. However, these issues are less prominent in the context of epidemiological interventions, especially epidemics, for which there is generally a much shorter and well-defined time frame for both monitoring and control.

Finally, even if the context is appropriate and the benefit of AM well understood, implementation still remains a challenge [14, 83]. Most approaches involve the use of stochastic dynamic programming and Markov decision processes, as described above, with uncertainty updated using a Bayesian procedure. However, in the context of epidemiological interventions, where the space of possible controls and outcomes is incredibly large, such methods can become intractable. In this thesis, we focus on simplified examples with reduced options for control and uncertainty and a discretised state space. This helps to focus on what AM can be used to optimise and the relevant information that it can provide to decision makers, without being limited by computational capacities. We revisit the computational difficulties of implementation in detail in the discussion.

Applications

Despite the difficulties surrounding the implementation of AM in practice, there have been a small number of successful AM projects in a range of ecological scenarios. Notably, the use of active AM has led to multiple large-scale flow experiments along

the Glen Canyon Dam section of the Colorado River, allowing significant advances in knowledge relating to the location of sediment deposits and interaction between species within this ecosystem [49, 84, 85]. As a direct result of these experiments, ecologists have been able to improve the management of this waterway, decreasing variation in water availability and increasing biodiversity in the area. Another well documented example of active AM in use is in the management of waterfowl populations in the United States [50]. By experimenting with different rates of harvesting in a rigorous, structured way, ecologists were able to better inform the relationship between harvest and survival rates, allowing for greater optimisation of harvesting practices without endangering this ecosystem.

Other examples include the control of animal populations [86–88], as well as native animal reintroductions [89, 90] and pest and predator control [91, 92]. Also the protection of environments such as wetlands [50, 77, 78, 93, 94], forests [95–99] and woodlands [100], the use of dams and the restoration of mining sites [101] to help restore and maintain local wildlife populations and biodiversity [102]. However, compared to the theoretical applications that have been explored in the literature, this is a very small percentage of possible projects [47, 48].

AM has yet to be applied in practice in the context of epidemiological interventions, however it has recently gained attention in the literature [11, 51, 56, 103]. In conjunction with Value of Information methods (next section), it has been shown to improve control outcomes in a number of scenarios. Similar applications, though not explicitly described as AM, have also shown the benefit of adaptive control and uncertainty resolution in a structured way [6, 21, 31, 104–109].

This thesis provides a significant exploration of AM in the context of epidemic control, not yet seen in the literature, with a range of generalisable examples common to this field. We clearly demonstrate the difference between a passive and active approach to management in this context, motivating the use of the latter. We then show that active AM can provide significant benefits over non-adaptive or passive approaches, including improved management outcomes, more efficient monitoring and providing state- and time-dependent policy recommendations, with the consequences of different control policies and levels of uncertainty resolution clearly portrayed. Overall, we show that epidemic control is an appropriate and worthwhile application of the AM framework that warrants further exploration and practical implementation.

2.2 Value of Information

Value of Information (VoI) analysis is a branch of decision theory that aims to quantify the benefit of resolving uncertainty in a system on the outcome of decisions made that affect the state of the system. It has been in use since its introduction by Raiffer and Schlaifer in 1961 [110] and has received significant technical attention, with notable contributions from Howard [111–113], Thompson and Graham [114], Felli and Hazen [115, 116] and Yokota and Thompson [117]. It has been applied in a wide range of fields, examples including public health [118–120], environmental management [121, 122], conservation ecology [123–125] and recently in epidemiology [11, 107, 126, 127]. In VoI analyses, information gain is not explicitly associated with a reward, but can lead to improved decisions, thus adding value. This ideology is mirrored in AM, especially active AM, hence, combining VoI with the AM framework has also received attention in the literature [11, 124, 125]. We build upon this idea throughout this thesis, using several ideas from the VoI field within the AM framework. Here, we introduce three measures used in VoI analysis that will be referred to throughout.

Expected value of perfect information (EVPI)

In general, VoI measures calculate the difference between the expected outcome given new information and the expected outcome under the current level of information. The first measure we introduce, the expected value of perfect information (EVPI), is the simplest to calculate and most widely used. It assumes that the new information obtained results in complete resolution of all uncertainties in the system; that is, we have perfect information. Mathematically, we calculate EVPI using Equation 2.3 [117]:

$$EVPI = \mathbb{E}_s[\max_a U(a, s)] - \max_a \mathbb{E}_s[U(a, s)], \tag{2.3}$$

where $U()$ is a utility function which we want to maximise by implementing some action a in the presence of system uncertainty s. The first half of the equation represents the expected outcome with perfect information: for every possible value of s, we choose a such that the utility is maximised. The second half of the equation represents the expected outcome with the current level of information: we choose a single a that maximises the expected utility across all values of s. The calculation of expectations depends on the current level of information regarding s, such that values of s that are deemed more probable contribute a greater weight.

In Chapter 4, we extend this measure to incorporate a notion of time (that is,

when we obtain perfect information), enabling greater analysis of monitoring delays and optimal monitoring strategies.

Expected value of perfect partial information (EVPXI)

The second measure, the expected value of perfect partial information (EVPXI) [117], assumes that there is more than one source of uncertainty in the system. In contrast to EVPI, in this measure we only gain perfect information for a subset of these uncertainties. For example, if we assume that s is a set of parameters that are uncertain, s_i a subset of these parameters for which we attain perfect information and s_i^c the complement, then:

$$EVPXI_{s_i} = \mathbb{E}_{s_i}[\max_a \mathbb{E}_{s_i^c}[U(a,s)]] - \max_a \mathbb{E}_{s_i,s_i^c}[U(a,s)], \tag{2.4}$$

where $U()$ is a utility function which we wish to maximise by implementing some action a, as before. The difference between Equation 2.3 and Equation 2.4 is in the first half of the equations, when calculating the expected outcome with new information. For EVPXI, there still remains uncertainty in the parameters contained in s_c^i, therefore we choose an action a that maximises the expected utility over this set of parameters, conditioned on a given value of the parameters in s_i.

Expected value of sample / imperfect information (EVSI / EVII)

A significant drawback of the EVPI and EVPXI measures is the assumption that the uncertainty in at least a subset of the parameters will be completely resolved. This is unrealistic in most contexts, especially in inherently stochastic systems such as epidemiological models. This final measure, the expected value of sample / imperfect information (EVSI / EVII; used interchangeably throughout the literature) [117], takes this into account. Rather than assuming that new information results in perfect information regarding system parameters, we instead construct a posterior distribution for parameters that depends on both the prior information and some data, or sample information, x, and choose the best action based on this posterior. However, since x has not yet been observed, we must do so for all possible observations of this data:

$$EVSI = EVII = \mathbb{E}_x[\max_a \mathbb{E}_{s|x}[U(a,s)]] - \max_a \mathbb{E}_s[U(a,s)]. \tag{2.5}$$

Whilst this measure is more realistic, it is significantly more computationally and theoretically intensive, requiring calculation across a large number of possible obser-

vations x as well as a method of quantifiying the probability of such observations occurring. However, in Chapter 4, we demonstrate the benefits of using this type of method within the AM framework compared to the EVPI measure which is easier to calculate but requires the significant assumption of perfect information.

2.3 Parameter inference

Parameter inference plays an important role in the AM framework, allowing us to prescribe how incoming data from the outbreak may affect the uncertainty surrounding parameters within the system. Furthermore, in order to calculate the expected outcomes of implementing an action using a utility averaged approach, it is necessary that we define uncertainty probabilistically. As such, a Bayesian approach to parameter inference is most appropriate, as opposed to Maximum Likelihood type approaches that focus mainly on providing point estimates. In this section, we give a brief overview of Bayesian inference, Markov chain and Hamiltonian Monte Carlo methods and implementation using the Stan software package.

2.3.1 Bayesian inference

Bayesian inference methods have become a powerful and ubiquitous tool for epidemiological modellers in the past two decades, especially in the area of real-time forecasting and parameter estimation (e.g. [10, 17, 33]). The advantage of these methods is the ability to estimate continuous probability distributions for model parameters, dependent on both prior knowledge and observed data. Formally, given uncertain parameters θ, a prior distribution $\pi(\theta)$ and observed data from the model D, we are able to determine the posterior distribution $f(\theta \mid D)$ using Bayes' Theorem:

$$f(\theta \mid D) \propto L(D \mid \theta)\pi(\theta), \tag{2.6}$$

where $L(D \mid \theta)$ represents the likelihood of observing such data D conditioned on given parameters θ. The prior distribution $\pi(\theta)$ can be informative, based on historical outbreaks or biological research, or uninformative, taking a non-specific distribution with a high variance. In Chapter 3, we show how the definition of the prior can affect our ability to use real-time information to improve control.

Thus, using Equation 2.6, we are able to recalculate and resolve uncertainty regarding system parameters in light of new information gathered from an outbreak. However, depending on the form of the likelihood ($L(D \mid \theta)$) and prior ($\pi(\theta)$), it may

be difficult to solve Equation 2.6 analytically. In such instances, it is necessary to rely on numerical methods to estimate the posterior, such as MCMC.

Markov chain Monte Carlo

Markov chain Monte Carlo (MCMC) methods have been used by epidemiologists since their introduction in the late 1990s [128–133] to estimate the posterior $f(\theta \mid D)$ when Equation 2.6 can not be solved analytically, providing samples from an equivalent target distribution. The fundamental idea underlying MCMC is to generate a Markov chain whose stationary distribution is the target distribution $f(\theta \mid D)$. Most MCMC methods rely on the following basic steps:

1. Begin with an initial sample θ
2. Propose a new sample, θ', using a proposal distribution q that depends on the current sample
3. Accept the new sample with probability α that depends on the current and proposed sample, otherwise reject and keep current sample
4. Repeat from step 2, until a sufficient number of samples have been generated

The proposal distribution q and acceptance probability α depend on the exact method used. One common method is the Metropolis-Hastings algorithm, for which q is often a Gaussian distribution with mean θ and arbitrary variance σ, and α is calculated via:

$$\alpha = \min\left\{1, \frac{L(D \mid \theta')\pi(\theta')q(\theta \mid \theta')}{L(D \mid \theta)\pi(\theta)q(\theta' \mid \theta)}\right\}. \tag{2.7}$$

In essence, we propose a new sample based on the current sample with some added noise, then, if the observed data is more probable given the new sample compared to the current sample, we definitely accept it, otherwise we accept it with a probability less than 1. Accepting a new sample that is less probable than the current sample is necessary to allow better exploration of the parameter space.

The main drawback of this type of sampling is that new samples are generally close to the current sample. As a result, if the target distribution is distant from the initial state, or if the target distribution has multiple modes or an unusual shape, it can take a long time for such algorithms to converge to the stationary distribution or properly explore the parameter space.

Hamiltonian Monte Carlo

Hamiltonian, or Hybrid, Monte Carlo (HMC) methods [134] are similar to MCMC methods, but do not implement a random walk to generate samples. Instead, they rely on the 'physical' properties of the target distribution, which enables larger, adaptive step sizes between samples. The HMC algorithm combines samples from the parameter space with a 'momentum' variable (ρ), usually drawn from a multivariate normal distribution with mean 0 and covariance matrix Σ. The joint density of both the parameter sample and momentum variable, $p(\rho, \theta)$, is used to define the Hamiltonian function, H, as the negative logarithm of the joint density:

$$H(\rho, \theta) = -\ln(p(\rho, \theta)) = -\ln(p(\rho \mid \theta)) - \ln(p(\theta)) = T(\rho \mid \theta) + V(\theta).$$

The Hamiltonian can be interpreted, using intuition from physics, as the sum of the kinetic energy T, from the momentum variables, and the potential energy V, or location, of the current sample. Together, H is the total energy of the system. The system then evolves according to Hamilton's equations:

$$\frac{d\theta}{dt} = \frac{\partial T}{\partial \rho},$$
$$\frac{d\rho}{dt} = -\frac{\partial V}{\partial \theta}.$$

Note that the second equation is simplified using the assumption that the momentum is independent of the sample. This system of equations is solved numerically, often using a leapfrog algorithm. Such a method requires a number (L) of small, discrete steps through time (ϵ), updating θ and ρ along the way. The parameters L and ϵ must be tuned and can have a significant effect on the performance of HMC. If ϵ is too small, it will take a long time to evolve the system from one sample to the next, however if ϵ is too large, the leapfrog integration results are likely to be inaccurate. Similarly, if L is too large, the algorithm will take a long time, but if L is too small, it begins to behave in the same way as a random walk MCMC type method.

The final step is a Metropolis acceptance step, similar to that within MCMC methods. Here, the new sample, (ρ^*, θ^*), is accepted with a probability α that depends on the change in total energy in the system (i.e. the Hamiltonian). This helps to bound errors that arise during the leapfrog numerical integration step:

$$\alpha = \min\left\{1, \exp(H(\rho, \theta) - H(\rho^*, \theta^*)\right\}.$$

Overall, HMC allows for larger steps between samples, therefore requiring fewer

iterations to generate uncorrelated samples, allowing for faster exploration and convergence to the target distribution than traditional MCMC methods (assuming appropriately tuned parameters).

2.3.2 Stan

Stan is a modern software package aimed towards statistical modelling and computation [135]. It has a range of capabilities, though for this thesis we have only used it to perform Bayesian inference with HMC sampling. Stan programs are written in their own language, then translated into C++ and compiled, often resulting in significantly faster computation compared to those written in Python or R. Stan is easily interfaced with most popular computing languages, including Python (PyStan), R (RStan), MATLAB (MatlabStan) and Julia (Stan.jl). We use PyStan to perform sampling procedures from our Stan models and analyse the results.

Blocks

Every Stan program consists of a number of blocks, containing variable declarations and in some cases statements. The simplest inference procedures will be made up of at least three blocks:

`data` - declare all known variables and parameters, including observed data. Anything declared in this block must be passed to the Stan program when called.

`parameters` - declare the unknown parameters. The program will aim to produce posterior distributions for anything declared here.

`model` - state the prior distributions for unknown parameters and the log-likelihood function for the observed data.

Other additional blocks can be added to the program to increase the complexity. Of particular note to epidemiologists are:

`functions` - allowing for user-defined functions, such as a system of ODEs describing the spread of a disease.

`transformed parameters` - allowing intermediate variables to be calculated from data and parameters. Within this block, it is possible to use Stan's inbuilt ODE solvers to obtain a simulation of an epidemic based on a sample of the parameters.

`generated quantities` - can be used to generate quantities that depend on the parameters, such as the total number of infections from an outbreak or the R_0 at a

specified point in time. This block does not affect the inference.

Sampling

A combination of blocks constitutes a Stan model which, once compiled, can be used to sample from the posterior. Stan uses HMC sampling, as described in the previous section, resulting in a highly efficient sampling procedure. Specifically, it uses a sampling algorithm known as the no-U-turn sampler (NUTS) [136]. This allows automatic tuning of the parameters required for HMC: the number of leapfrog steps L, the size of each step ϵ and the covariance matrix Σ used to generate momentum variables. In simple terms, the NUTS algorithm will continue to make leapfrog steps until either a maximum number of steps is reached, or the trajectory in the parameter space begins to turn back on itself (hence, no-U-turns). This allows for an adaptive number of steps L. The other two parameters, ϵ and Σ, are estimated during the warm-up phase in order to achieve a target acceptance rate.

Chapter 3

A comparison of active and passive adaptive management

Abstract

We introduce and compare three approaches to managing an epidemic: non-AM, passive AM and active AM. These approaches differ in how they incorporate real-time information from the outbreak to resolve uncertainty. A non-AM approach does not use real-time information to resolve uncertainty, relying solely on prior information. A passive AM approach will use real-time information in a reactive way, resolving uncertainty if and when new information becomes available, but not anticipating it. Finally, an active AM approach anticipates the resolution of uncertainty in the future, explicitly incorporating it into current control decisions. Using a simplified, theoretical epidemic, we find that decisions regarding vaccination as control can be non-trivial if the vaccine efficacy is unknown. Furthermore, the three approaches we compare can lead to different control decisions and thus epidemic outcomes. Overall, we find that active AM is the most useful approach for providing effective policy recommendations to decision makers.

3.1 Introduction

In this chapter, we investigate how different methods of including real-time information can affect policy selection during an epidemic and, in turn, how this affects our ability to satisfy the objectives of management. We compare three approaches to managing a theoretical epidemic: non-AM, passive AM and active AM. The

epidemic is represented by a deterministic, non-spatial Susceptible-Exposed-Infected-Recovered (SEIR) compartmental model, with control limited to vaccination of the susceptible population at a fixed daily vaccination rate, restricted by a finite vaccine pool. There is no uncertainty regarding the spread of the disease in the absence of control, however a single source of uncertainty is introduced through an unknown vaccine efficacy, defined as the probability that an administered vaccine will result in immunity. Information regarding the vaccine efficacy can be collected throughout the outbreak by monitoring a proportion of administered vaccines for success: a successful vaccination results in complete, indefinite immunity that takes effect, and can be tested, immediately. Conversely, we assume that unsuccessful vaccinations result in no immunity.

The non-AM approach represents a static control policy, in which real-time information is not used to improve control. Under this approach, there is a single decision opportunity at the start of the outbreak (day 0), for which we must decide whether to implement a vaccination campaign or not. This approach represents a standard SDM [53] approach and provides a baseline for the performance of control. The passive and active AM approaches allow for adaptation of control on a single, predetermined day during the outbreak (t^*). For these approaches, there are two decision opportunities: the initial decision on day 0 and a final decision on day t^*. The initial decision is whether or not to implement a vaccination campaign immediately and continue it until at least day t^*. The final decision is whether or not to vaccinate from day t^* until the vaccine pool is depleted

For the initial decision, we have only the 'prior information' regarding vaccine efficacy. On day t^*, the results of monitored vaccinations, if any vaccinations have been administered, are used to provide updated information regarding vaccine efficacy. Hence, an initial decision to vaccinate allows for the resolution of uncertainty in vaccine efficacy, whilst an initial decision not to vaccinate does not. Passive AM does not incorporate the effect of reducing uncertainty in the vaccine efficacy into the initial decision, hence, whilst this information might be used for the final decision, we do not plan to use it. As such, passive AM represents a reactive approach to incorporating real-time information. Active AM explicitly incorporates the resolution of uncertainty into its initial decision recommendation. Therefore, if choosing to vaccinate, thereby allowing uncertainty in vaccine efficacy to be reduced, leads to significantly improved future management, active AM will recognise this and choose to vaccinate immediately.

For the basis of this analysis, we focus on two scenarios, contrasted primarily by different management objectives. Scenario 1: we allocate a 'cost' to the epidemic,

defined by a linear combination of the number of infections, vaccines administered and a fixed cost associated with implementing a vaccination campaign. The objective of management is to minimise the expected value of this cost. This scenario could be likened to a non-fatal, human disease context, or livestock disease context, where the cost of implementing a vaccination campaign must be weighed against the expected benefits resulting from the campaign. In this scenario, we parametrise the epidemic model using influenza-like transmission, incubation and recovery rates, with a basic reproductive number (R_0) of 1.6. The relative weights of infections and vaccinations in the calculation of cost are fixed for the main result, however the effect these have on the result is explored in detail in the subsequent sensitivity sections.

Scenario 2: the objective of management is to minimise the expected duration of the outbreak, regardless of the number of infections caused or vaccines used. This scenario could be likened to a livestock disease context in which there are significant daily costs to the economy caused by an ongoing outbreak, such as loss of exports or tourism. In such a context, regaining a 'disease-free' status as quickly as possible may be the primary concern. In this scenario we parametrise the epidemic model with Foot-and-Mouth-like transmission, incubation and recovery rates, with an R_0 of 2. For both scenarios, the effect of changing the epidemiological parameters used and the restrictions on control is explored in detail.

For both scenarios, we initially assume a large amount of uncertainty in the vaccine efficacy at the start of the outbreak, or equivalently, a very low amount of prior information. The effect of having more prior information to inform our decisions is also explored in detail.

We investigate the policy selection and performances of the three approaches for the two specific scenarios, showing that the method of incorporating real-time information can have a significant effect. We also show how this changes under different conditions, varying the amount of prior and real-time information available from the outbreak, restrictions on control and epidemiological parameters. Our focus on how passive approaches can lead to different control recommendations compared to active approaches, specifically in the the context of infectious disease epidemics, extends similar explorations in the ecological literature [58, 137]. Overall, we see that even highly simplified systems can be difficult to control in the presence of uncertainty and the method of incorporating real-time information into management decisions can have a significant effect on policy selection. We find that active AM is best able to meet management objectives, whilst also providing more usable information to decision-makers with regards to the collection of real-time information and the timing and delivery of control.

3.2 Adaptive management components

3.2.1 Model of system behaviour

We describe the spread of a directly transmitted disease throughout a population via a non-spatial, homogeneously mixing, deterministic SEIR (Susceptible, Exposed, Infected, Recovered/Removed) model, with constant transmission rate (β), incubation rate (σ) and recovery/removal rate (γ; this can include both recovery and death from the disease). We ignore demography on the assumption that the dynamics of the epidemic are significantly faster than the natural birth-death process of the population. The transmission, incubation and recovery rates used in each scenario are provided in Table 3.1. For both scenarios, the initial population is made up of 5000 susceptible and 1 infected individual. We assume that the epidemic is not detected until the number of infected individuals reaches 20. We denote t as the number of days since the epidemic was detected, with $t = 0$ representing the day of detection and initial management decision.

Control is limited to vaccination of the susceptible population. We assume that vaccinations are perfectly targeted towards susceptible individuals, excluding the exposed class from vaccination, to help clarify the link between uncertainty in vaccine efficacy and the predicted outcome of control. Vaccinations can occur at a constant daily rate (ν_r; number of vaccinations per day), restricted by a limit on the total number of vaccines available (ν_{pool}). The vaccine is assumed to result in immediate and indefinite immunity, with probability ν_e. This probability, the 'vaccine efficacy', is unknown and provides the only source of uncertainty in the system. If the vaccine is successful, the vaccinated individual moves into compartment V_1, where it remains indefinitely. Else, if the vaccine is unsuccessful, the individual moves into compartment V_0, where it remains susceptible to infection but is not able to receive a second dose of the vaccine.

The differential equations for the system are stated in Equation 3.1 and a schematic can be found in Figure 3.1:

$$
\begin{aligned}
\frac{dS(t)}{dt} &= -\beta\frac{S(t)I(t)}{N(t)} - \nu_r(t),\\
\frac{dE(t)}{dt} &= \beta\frac{(S(t)+V_0(t))I(t)}{N(t)} - \sigma E(t),\\
\frac{dI(t)}{dt} &= \sigma E(t) - \gamma I(t),\\
\frac{dR(t)}{dt} &= \gamma I(t),\\
\frac{dV_0(t)}{dt} &= (1-\nu_e)\nu_r(t) - \beta\frac{V_0(t)I(t)}{N(t)},\\
\frac{dV_1(t)}{dt} &= \nu_e\nu_r(t),
\end{aligned}
\tag{3.1}
$$

where $\nu_r(t)$ depends on the current vaccination campaign. We denote the vaccination campaign $\mathcal{V}_{t_i,t_j}$, representing a campaign that starts on day t_i and ends on day t_j. If $t_i \leq t \leq t_j$, the campaign is ongoing and

$$
\nu_r(t) = \begin{cases}
\nu_r, & \text{if } S(t) \geq \nu_r,\\
S(t), & \text{if } 0 \leq S(t) < \nu_r,\\
\nu_{pool} - \int_{t_i}^{t} \nu_r(s)\mathrm{d}s, & \text{if } \nu_{pool} - \int_{t_i}^{t} \nu_r(s)\mathrm{d}s < \nu_r,\\
0, & \text{if } \int_{t_i}^{t} \nu_r(s)\mathrm{d}s > \nu_{pool}.
\end{cases}
\tag{3.2}
$$

If $t < t_i$ or $t > t_j$, the campaign is not currently ongoing and $\nu_r(t) = 0$. If no vaccination occurs throughout the epidemic, we denote this by $\mathcal{V}_{0,0}$. Note that $\nu_r(t)$ may also depend on the vaccine efficacy ν_e, through the depletion of S; we emphasise this with the notation $\nu_r(t, \nu_e)$ where necessary.

Finally, t_{end} represents the day on which the outbreak ends and hence the duration of the outbreak (relative to the time of detection). This also depends on the vaccination campaign chosen and vaccine efficacy. Given the continuous nature of the differential equations (Equation 3.1), we define this to be the point at which the number of Exposed and Infectious individuals together falls below 1 ($E(t)+I(t) < 1$).

A description of the parameters and their default values throughout this chapter (unless otherwise specified) can be found in Table 3.1.

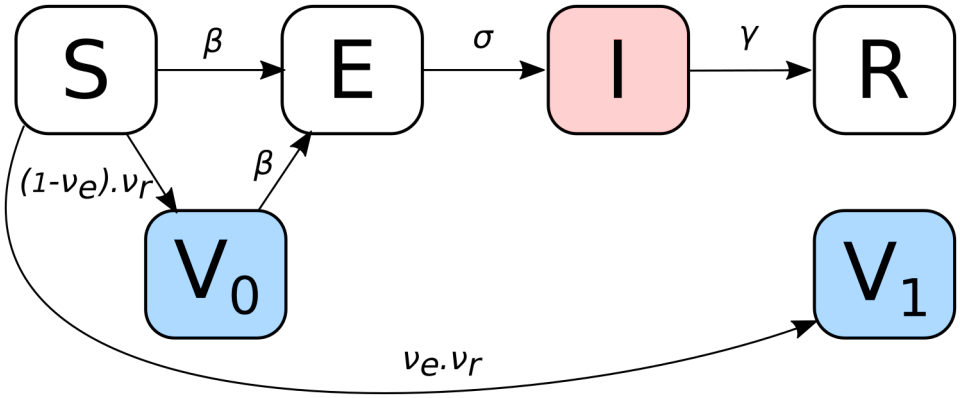


Figure 3.1: **Model of system behaviour.** We use a non-spatial, homogeneously mixing, deterministic Susceptible-Exposed-Infected-Recovered (SEIR) model with vaccination as control. The transmission (β), incubation (σ) and recovery (γ) rates are constant throughout the epidemic. If a vaccination campaign is active, vaccination will occur at a constant daily rate ν_r (number of individuals per day), subject to the conditions outlined in Equation 3.2. The vaccine is perfectly targeted towards only Susceptible individuals. If a Susceptible individual is vaccinated, it will be effective with probability ν_e and they will gain full, indefinite immunity immediately, moving to compartment V_1. If ineffective, they move to compartment V_0, where they remain fully susceptible to the disease but can not be vaccinated again. Blue shaded compartments identify vaccinated individuals and red shaded compartments infectious individuals.

Table 3.1: **Summary of parameters and notation used.** Scenario specific values apply throughout unless otherwise stated in the sensitivity sections. Values left blank depend on the vaccination campaign and are calculated as required during the optimisation process.

Notation	Description	Sc. 1	Sc. 2
β	Transmission rate of disease	0.23	0.2
σ	Incubation rate of disease	0.5	0.2
γ	Recovery/removal rate from disease	0.14	0.1
ν_r	Daily vaccination rate (number of individuals)	100	100
ν_e	Vaccine efficacy	$[0, 1]$	$[0, 1]$
ν_{pool}	Total number of vaccines available	2500	4500
t^*	Time of final decision point	7	7
t_{end}	Day on which outbreak ends (duration of the outbreak)	-	-
$\mathcal{V}_{t_i,t_j}$	Denotes a vaccination campaign that starts on day t_i and ends on day t_j. We require $0 \leq t_i \leq t_j \leq t_{end}$	-	-
$C(X \mid a_0, a_1, \nu_e)$	Cost of an outbreak, conditioned on the initial and final decisions (leading to vaccination campaign $\mathcal{V}_{t_i,t_j}$) and vaccine efficacy. Dependence on epidemiological parameters is excluded for brevity.	-	-
ω_1	Weight assigned to the length of the outbreak (per day) in calculation of cost	0	1
ω_2	Weight assigned to each infection caused by the outbreak in calculation of cost	1	0
ω_3	Weight assigned to each vaccination administered in calculation of cost	0.6	0
ω_4	Weight associated with a fixed cost of implementing a vaccination campaign in calculation of cost	350	0
x_0	Number of successful vaccinations that form prior information regarding vaccine efficacy	0.1	0.1
y_0	Number of unsuccessful vaccinations that form prior information regarding vaccine efficacy	0.1	0.1
ρ	Proportion of administered vaccines monitored for success	5%	5%
M_t	Number of vaccines monitored for success until time t	-	-
x_t	Number of successful, monitored vaccinations up to time t	-	-
y_t	Number of unsuccessful, monitored vaccinations up to time t	-	-
N	Total population size	5000	5000

3.2.2 Objectives of management

The objective of management differs between the two scenarios, however can be summarised in general terms by defining a flexible cost function that incorporates multiple factors: the duration of the outbreak, the number of vaccines administered, a fixed cost associated with implementing a vaccination campaign and the number of infections caused by the epidemic. The cost of the outbreak is calculated using a weighted, linear combination of these factors. Given initial and final decisions a_0 and a_1, resulting in a campaign $\mathcal{V}_{t_i,t_j}$ with efficacy ν_e (and epidemiological parameters; excluded from notation for brevity), the cost of an outbreak X is:

$$\begin{aligned} C(X \mid a_0, a_1, \nu_e) = \omega_1 \, t_{end}(\nu_e) \; + \; \omega_2 \left(\int_0^{t_{end}(\nu_e)} I(s, \nu_e) \mathrm{d}s \right) \\ + \omega_3 \left(\int_{t_i}^{t_j} \nu_r(s, \nu_e) \mathrm{d}s \right) + \omega_4 \, \delta_V . \end{aligned} \tag{3.3}$$

where

$$\delta_V = \begin{cases} 1, & \text{if a vaccination campaign is implemented,} \\ 0, & \text{otherwise.} \end{cases} \tag{3.4}$$

The cost in scenario 1 is defined by using non-zero weights for ω_2, ω_3 and ω_4 and setting $\omega_1 = 0$ (that is, a combination of vaccine and infection costs). For scenario 2, we let $\omega_2 = \omega_3 = \omega_4 = 0$ and $\omega_1 = 1$ (duration only). The weights, ω_i, can either be unitless, representing the relative importance of each, or take a unit such as currency. For example, ω_1 may be the daily loss of income to the economy from reduced tourism or exports during the epidemic, ω_2 the total cost of care of an infected human or loss of profit from having livestock infected, ω_3 the average monetary cost of transporting and administering each vaccine and ω_4 the cost of developing a new vaccine and marketing the campaign. The default weights used for the basis of each scenario are given in Table 3.1, selected to make the initial decision non-trivial. However, our flexible definition of the cost allows us to easily explore the ramifications of having different objectives in later sensitivity sections.

In both scenarios, the objective of management is to minimise the expected cost of the outbreak. This expectation is calculated by integrating over the probability distribution around vaccine efficacy (Equation 3.5). This distribution, $f(\nu_e)$, is

defined in the next section.

$$\mathbb{E}[C(X \mid a_0, a_1)] = \int_0^1 C(X \mid a_0, a_1, \nu_e) \cdot f(\nu_e)\, \mathrm{d}\nu_e. \tag{3.5}$$

We approximate the integral in Equation 3.5 by binning vaccine efficacy into 1% intervals.

3.2.3 Prior information and monitoring

Prior and real-time information focuses on resolving the uncertainty in the system introduced by an unknown vaccine efficacy (ν_e). We define this information in a quantitative manner.

We define the prior information regarding vaccine efficacy using a $Beta(x_0+1, y_0+1)$ distribution, where $x_0, y_0 \geq 0$. Hence, the probability density function is:

$$f(\nu_e; x_0, y_0) = \frac{\Gamma(x_0 + y_0 + 2)}{\Gamma(x_0 + 1)\Gamma(y_0 + 1)} \nu_e^{x_0} (1 - \nu_e)^{y_0}, \tag{3.6}$$

where $\Gamma(\cdot)$ is the Gamma function. The mode of the distribution, $\frac{x_0}{x_0+y_0}$, corresponds to the estimate of vaccine efficacy. The sum $x_0 + y_0$, also known as the concentration [59], relates to the amount of information that is supporting the estimate and is inversely related to the variance. For example, if the prior information is from a historical vaccine trial, x_0 could be the number of successful vaccinations and y_0 the number of unsuccessful vaccinations from the trial. However, to allow non-integer values of x_0 and y_0 in our analysis, we define the sum $x_0 + y_0$ to be the relative strength of the prior information compared to a single monitored vaccination (introduced below). If there is no prior information ($x_0 = y_0 = 0$), the distribution is uniform between 0 and 1 and hence the mode is undefined. For the majority of this analysis, except when explicitly investigating the effect of prior information on our management decisions, we set $x_0 = y_0 = 0.1$ (Table 3.1) when defining our prior distribution around vaccine efficacy. This results in a distribution centred around 50% efficacy with a large variance, representing a situation where we do not have a strong idea of what the efficacy is, but are aware that it is less likely to be completely effective (100% efficacy) or completely ineffective (0% efficacy).

Real-time information is collected throughout the outbreak by monitoring a proportion (ρ) of administered vaccinations for success. We assume that the success or failure of a vaccine can be tested immediately after it is administered and this test will always give the true result. Whilst this is an unrealistic assumption, it

allows us to clearly identify the relationship between monitored vaccinations and the resolution of uncertainty in vaccine efficacy. We denote M_t as the total number of vaccinations monitored up to time t, with x_t and y_t the number of successful and unsuccessful vaccinations respectively (hence $M_t = x_t + y_t$). This real-time information is combined with the prior information (using Bayes' formula and the conjugacy of the prior and likelihood) to give a posterior distribution around the vaccine efficacy, defined by a $Beta(x_0+x_t+1, y_0+y_t+1)$ distribution with probability density function:

$$f(\nu_e; x_0, y_0, x_t, y_t) = \frac{\Gamma(x_0 + x_t + y_0 + y_t + 2)}{\Gamma(x_0 + x_t + 1)\Gamma(y_0 + y_t + 1)} \nu_e^{x_0+x_t}(1 - \nu_e)^{y_0+y_t}. \tag{3.7}$$

3.2.4 Optimisation approaches

In this chapter, we compare three approaches to decision making during the outbreak: non-AM, passive AM and active AM. These approaches are contrasted by how they incorporate real-time outbreak information, in this case the results of monitored vaccinations. Under any of the three approaches, at each decision point we must choose to vaccinate until the next decision point or not. If there are no future decision points, this equates to vaccinating until the vaccine pool is depleted, or forgoing vaccination for the remainder of the epidemic. We allow a maximum of two decision points (one for the non-AM approach): an initial decision is made when the outbreak is detected (a_0 at $t = 0$) and a final decision is made on a predetermined day during the outbreak (a_1 at $t = t^*$). We denote the choice to vaccinate or not vaccinate vac and $\neg vac$ respectively.

Under the non-AM approach we allow only the initial decision. Under the adaptive approaches, a proportion of the vaccines administered between the initial and final decision points, if any, are monitored for success and this information is used to inform the final decision. The adaptive approaches differ in how they make the initial decision, with passive AM ignoring the effect that updated vaccine efficacy information may have on future decisions, whilst active AM explicitly accounts for this. The method of decision making at both decision points, under each management approach, is formalised below.

Non-AM

Initial decision ($\mathbf{t = 0}$) Under the non-AM approach, we are unable to change our decision at t^*. Hence, we assume that $a_1 = a_0$: a choice to vaccinate now ($a_0 = vac$)

implies vaccination until vaccine pool depletion and a choice not to vaccinate now ($a_0 = \neg vac$) implies forgoing vaccination until the epidemic is over. We compare the two choices of initial decision by the expected cost of the outbreak resulting from each (Equation 3.8), choosing that which produces the lowest expected cost over the prior distribution around vaccine efficacy ($f(\nu_e; x_0, y_0)$):

$$\mathbb{E}[C(a_0)] = \mathbb{E}[C(X \mid a_0, a_1 = a_0)] = \int_0^1 C(X \mid a_0, a_1 = a_0, \nu_e) \cdot f(\nu_e; x_0, y_0)\, \mathrm{d}\nu_e, \tag{3.8}$$

where $a_0 = a_1 = vac$ leads to campaign $\mathcal{V}_{0,t^*}$ and $a_0 = a_1 = \neg vac$ leads to campaign $\mathcal{V}_{0,0}$.

Passive AM

Initial decision ($\mathbf{t = 0}$) Since there is a single future decision point at $t = t^*$, a choice to vaccinate initially ($a_0 = vac$) implies vaccination until at least t^*, followed by either vaccination ($a_1 = vac$, leading to the campaign $\mathcal{V}_{0,t_{end}}$) or no vaccination ($a_1 = \neg vac$, leading to the campaign $\mathcal{V}_{0,t^*}$). Note that we assume the ratio between the number of vaccines available and the daily vaccination rate is such that the vaccine pool will not be depleted before day t^*. Similarly, a choice not to vaccinate initially ($a_0 = \neg vac$) can result in forgoing vaccination completely ($a_1 = \neg vac$; $\mathcal{V}_{0,0}$) or a delayed campaign starting on day t^* ($a_1 = vac$; $\mathcal{V}_{t^*,t_{end}}$). When calculating the expected cost of each initial action (Equation 3.9), we assume that future decisions will be made optimally, given the information we have. Under passive AM, we do not plan for monitoring, hence we do not incorporate the anticipation of future monitored vaccinations into our initial decision. Instead, we assume that future decisions will be made based on the current level of information, in this case the prior information. Hence, the expected cost of an initial action under passive AM is the minimum of the expected cost of the two campaigns that can result from it, calculated over the prior distribution around vaccine efficacy (Equation 3.9):

$$\begin{aligned}\mathbb{E}[C(a_0)] &= \min_{a_1 = \{vac, \neg vac\}} \left(\mathbb{E}[C(X \mid a_0, a_1)]\right), \\ &= \min_{a_1 = \{vac, \neg vac\}} \left(\int_0^1 C(X \mid a_0, a_1, \nu_e) \cdot f(\nu_e; x_0, y_0)\, \mathrm{d}\nu_e\right),\end{aligned} \tag{3.9}$$

Final decision ($\mathbf{t = t^*}$) We make the final decision based on both the prior information and monitored vaccinations, if there are any. Since there are no more future decision points, this is a simple expectation over two choices: $a_1 = vac$ or $a_1 = \neg vac$ (Equation 3.10). We choose the option that produces the lowest expected

cost over the posterior distribution around vaccine efficacy ($f(\nu_e; x_0, y_0, x_{t^*}, y_{t^*})$). Note that, if the initial decision was not to vaccinate ($a_0 = \neg vac$), there will be no monitored vaccinations, hence $x_{t^*} = y_{t^*} = 0$ and the posterior distribution of vaccine efficacy is equal to the prior.

$$\begin{aligned}\mathbb{E}[C(a_1 \mid a_0, x_{t^*}, y_{t^*})] &= \min_{a_1=\{vac,\neg vac\}} \left(\mathbb{E}[C(X \mid a_0, a_1, x_{t^*}, y_{t^*})]\right), \\ &= \int_0^1 C(X \mid a_0, a_1, \nu_e) \cdot f(\nu_e; x_0, y_0, x_{t^*}, y_{t^*})\, \mathrm{d}\nu_e.\end{aligned} \tag{3.10}$$

Active AM

Initial decision (t = 0) As under passive AM, a choice to vaccinate initially ($a_0 = vac$) implies vaccination until at least t^*, followed by either continued vaccination ($a_1 = vac$; $\mathcal{V}_{0,t_{end}}$) or no vaccination ($a_1 = \neg vac$; $\mathcal{V}_{0,t^*}$), and a choice not to vaccinate initially ($a_0 = \neg vac$) can result in forgoing vaccination completely ($a_1 = \neg vac$; $\mathcal{V}_{0,0}$) or a delayed campaign starting on day t^* ($a_1 = vac$; $\mathcal{V}_{t^*,t_{end}}$). When calculating the expected cost of each initial decision (Equation 3.11), we assume that future decisions will be made optimally, given the information we have. In contrast to passive AM, under active AM we explicitly incorporate the anticipation of results of future monitored vaccinations into our initial decision. Hence, we assume that future decisions will be made based on not only the prior information, but also the results of monitored vaccinations. Since we do not know what the results of monitored vaccinations will be, we take an expectation over all possible results, weighted by the likelihood of observing these results given the prior information we have. For each set of results, we assume that the future decision is made optimally based on the information those results provide. This is known as preposterior analysis [117]. Therefore, the expected cost of an initial action under active AM is the weighted sum of the minimum expected cost of the two campaigns that can result from it, calculated over the posterior distribution around vaccine efficacy for all possible outcomes from monitored vaccinations (Equation 3.11):

$$\begin{aligned}\mathbb{E}[C(a_0)] &= \sum_{x_{t^*}=0}^{M_{t^*}} \left(\min_{a_1=\{vac,\neg vac\}} \left(\mathbb{E}[C(X \mid a_0, a_1, x_{t^*}, y_{t^*})]\right) \right) \cdot f\left(x_{t^*}; M_{t^*}, x_0, y_0\right), \\ &= \sum_{x_{t^*}=0}^{M_{t^*}} \left(\min_{a_1=\{vac,\neg vac\}} \left(\int_0^1 C(X \mid a_0, a_1, \nu_e) \cdot f(\nu_e; x_0, y_0, x_{t^*}, y_{t^*})\, \mathrm{d}\nu_e \right) \right) \\ &\qquad \cdot f\left(x_{t^*}; M_{t^*}, x_0, y_0\right),\end{aligned} \tag{3.11}$$

where $y_{t^*} = M_{t^*} - x_{t^*}$ and $f\left(x_{t^*}; M_{t^*}, x_0, y_0\right)$ is the probability density function of a *Beta-Binomial* distribution with parameters M_{t^*}, x_0 and y_0. Note that with $M_{t^*} = 0$, as would be the case if the initial decision was not to vaccinate, this reduces to Equation 3.9. Hence, in the absence of any monitored vaccinations, passive and active AM are identical.

Note that Equations 3.9 and 3.11 follow directly from our general definition of an MDP in Equation 2.2: assuming two discrete time points $t = \{0, t^*\}$, a reward function $r(s_t, a, \theta) = 0$ if $t = 0$ or $C(X \mid a_0, a_1, \nu_e)$ if $t = t^*$, a belief state $b(\theta \mid s_0) = f(\nu_e; x_0, y_0)$ if $t = 0$ or $f(\nu_e; x_0, y_0, x_{t^*}, y_{t^*})$ if $t = t^*$ and a transition probability between states $p(s_{t^*} \mid s_0, a_0, \theta) = f(x_{t^*}; M_{t^*}, \nu_e)$. For passive AM (Equation 3.9), we assume that $x_{t^*} = y_{t^*} = 0$, thus we require only a single integration over the prior distribution for ν_e. For active AM (Equation 3.11), the *Beta* prior for ν_e and *Binomial* likelihood of observations x_{t^*}, given ν_e, combine into a single weighted sum using a *Beta-Binomal* distribution. Using these substitutions, the accumulated value $V_a(s_t, b(s_t))$ at $t = 0$ is equivalent to $\mathbb{E}[C(a_0)]$.

Final decision ($\mathbf{t = t^*}$) Since there are no future decision points, and hence no more opportunities to gather information and adapt control, the final decision under active AM follows the exact same methodology as under passive AM (Equation 3.10), conditional on the initial decision made. Note that, under active AM, we have already performed all the necessary calculations to make this decision. If the initial decision was to vaccinate, we will have monitored M_{t^*} vaccinations by day t^* and observed a given number of successes and failures, x_{t^*} and y_{t^*}, leading to a posterior distribution around vaccine efficacy. The expected costs of continuing or ceasing vaccination based on this posterior distribution ($\mathbb{E}[C(X \mid a_0, a_1, x_{t^*}, y_{t^*})]$) have already been calculated and compared within the calculation of the expected cost of the initial decision (Equation 3.11). Thus, rather than recalculating these expected costs, we are able to make the final decision immediately given the number of successful vaccinations on day t^*. This shows active AM's ability to provide state-dependent recommendations, not possible under passive AM.

If the initial decision was not to vaccinate, no new information has been gained and hence, as under passive AM, the campaign that produced the lowest expected cost under the prior distribution (Equation 3.9) would be chosen, without need for recalculation and comparison of these expected costs.

3.3 Scenario 1

In the first scenario, we test our ability to minimise the 'cost' of a theoretical epidemic. Cost is defined as a linear combination of the number of infections caused by the outbreak, number of vaccines administered and a fixed cost associated with implementing a vaccination campaign (if one is implemented). The weight of each contributing factor is defined relative to that of a single infection, hence $\omega_2 = 1$ (Methods: Objectives of management). For the majority of the analyses undertaken under this scenario we set $\omega_3 = 0.6$ and $\omega_4 = 350$ and assume that the epidemiological parameters are representative of a flu-like disease such that the transmission rate $\beta = 0.23$, the incubation rate $\sigma = 0.5$ and the removal/recovery rate $\gamma = 0.14$, with $R_0 = 1.6$. Vaccination is limited to 100 individuals per day, with a total pool of 2500 vaccines (out of a total population of 5000 individuals). These parameters are summarised in Table 3.1. Sensitivity to all these parameters is explored in detail in later sections.

With a maximum of two decision points ($t = \{0, t^*\}$), there are a maximum of four possible campaigns that may be implemented by the end of the outbreak (Figure 3.2): 1) $\mathcal{V}_{0,t_{end}}$, vaccination is implemented immediately and continued until the vaccine pool is depleted, 2) $\mathcal{V}_{0,t^*}$, vaccination is implemented immediately and stopped on day t^*, 3) $\mathcal{V}_{t^*,t_{end}}$, vaccination is delayed until day t^*, then performed until the vaccine pool is depleted, and 4) $\mathcal{V}_{0,0}$, no vaccines are administered during the outbreak. Under active and passive AM, all four of these campaigns are taken into consideration, whilst under the non-AM approach only campaigns (1) and (4) are considered.

Under the non-AM approach to management, the initial decision to vaccinate or not can not be adapted. Hence, an initial decision to vaccinate is equivalent to committing to a full vaccination campaign ($\mathcal{V}_{0,t_{end}}$; Figure 3.3 red line) and an initial decision not to vaccinate is equivalent to foregoing vaccination for the duration of the outbreak ($\mathcal{V}_{0,0}$; Figure 3.3 blue line). Thus, under this approach, the optimal policy is to not vaccinate initially, and throughout, since it provides a lower expected cost over the prior distribution around vaccine efficacy than a full campaign. There is no opportunity to adapt this, hence we would forego vaccination for the duration of the outbreak under this approach.

Under passive AM, we recognise that an initial decision to vaccinate or not can be adapted on day t^*. Passive AM plans for this adaptation based on the prior information regarding vaccine efficacy. Hence, an initial decision to vaccinate is assumed to lead to a final decision to also vaccinate, since, over the prior distribution,

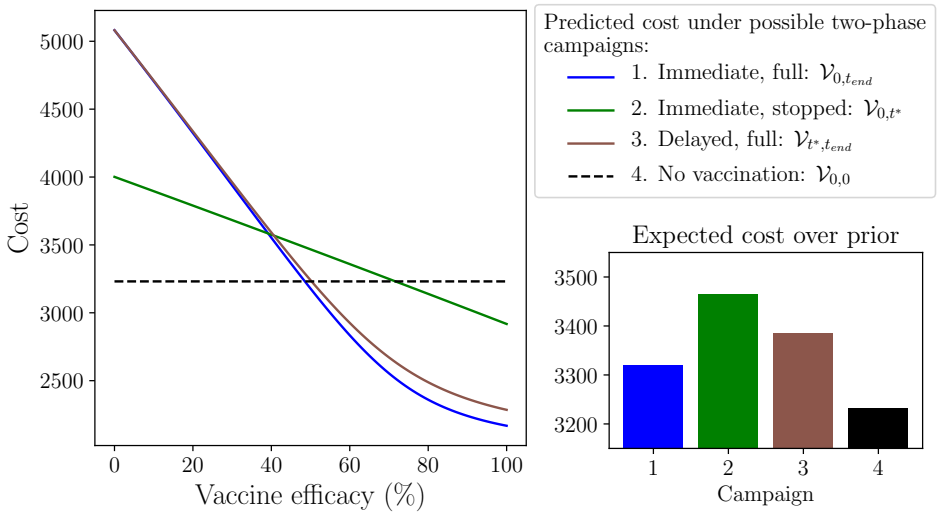


Figure 3.2: **Scenario 1: Predicted outbreak cost resulting from possible two-phase campaigns.** For the passive and active AM methods, the two decision points ($t = \{0, t^*\}$) result in four possible two-phase campaigns that may be implemented by the end of the outbreak: 1) vaccination is started immediately and continued until the vaccine pool is depleted, 2) vaccination is started immediately but stopped on day t^*, 3) vaccination is delayed until t^*, then continued until the vaccine pool is depleted, or 4) no vaccination is employed during the outbreak. The non-AM approach has only one decision point ($t = 0$), hence can only result in either campaign (1) or (4). Epidemiological and vaccination parameters are set to those in Table 3.1: Scenario 1. Expected cost is calculated over a $Beta(1.1, 1.1)$ prior distribution around vaccine efficacy.

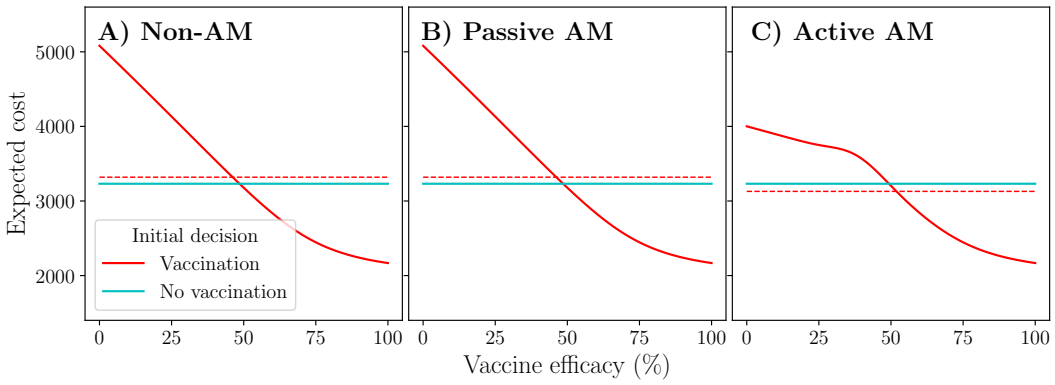


Figure 3.3: **Scenario 1: Expected outbreak cost resulting from an initial decision to vaccinate or not.** Expected outbreak cost from an initial decision to vaccinate (red) or not (blue), as viewed under non-AM (A), passive AM (B) and active AM (C) methods, conditional on the true value of efficacy. Dashed lines represent the expected cost calculated over a $Beta(1.1, 1.1)$ prior distribution around vaccine efficacy. Epidemiological and vaccination parameters are set to those in Table 3.1: Scenario 1.

stopping the campaign on day t^* would lead to a higher expected cost than continuing it (Figure 3.2). Thus, the expected cost of an initial decision to vaccinate is equivalent to the expected cost of an immediate, full campaign ($\mathcal{V}_{0,t_{end}}$) under passive AM (Figure 3.3 red line). Similarly, an initial decision not to vaccinate is assumed to always result in no vaccination throughout the outbreak, since a delayed, full campaign ($\mathcal{V}_{t^*,t_{end}}$) results in a higher expected cost than no vaccination throughout ($\mathcal{V}_{0,0}$) over the prior distribution (Figure 3.2). Hence, under passive AM, the expected cost of an initial decision not to vaccinate is equivalent to the expected cost of foregoing vaccination completely (Figure 3.3 blue line). Therefore, the optimal policy for passive AM is an initial decision not to vaccinate, since the expected cost of not vaccinating throughout is less than the expected cost of an immediate, full campaign. Since we do not have any vaccinations to monitor, no new information is available on day t^* and thus the final decision will also be to not vaccinate.

Under active AM, we again recognise that an initial decision to vaccinate or not can be adapted on day t^*, but also that this will depend on the results of monitored vaccinations. Hence, an initial decision to vaccinate is assumed to lead to continued vaccination if the success rate from monitored vaccinations is sufficiently high (larger than approximately 40%, based on the parameters we have chosen), otherwise vaccination will be stopped on day t^*. Thus, the expected cost of an initial decision to vaccinate is derived from a combination of campaigns 1 and 2 (Figure 3.3 red line): if the true vaccine efficacy is low, we are likely to get a low success rate from monitored vaccinations and stop the campaign, whereas if true efficacy is high the opposite will occur. Close to the value of vaccine efficacy where the cost of stopping and continuing the campaign cross over (approximately 40%), there is still uncertainty as to which choice is optimal even with the results from monitored vaccinations, hence the expected cost is increased slightly by the possibility of making the wrong final decision. In contrast, an initial decision not to vaccinate results in there being no vaccinations to monitor. Hence, as under passive AM, the expected cost of such an initial decision is equivalent to the expected cost of foregoing vaccination for the entire outbreak ($\mathcal{V}_{0,0}$; Figure 3.3 blue line). The optimal policy for active AM is to vaccinate initially, since the benefit from learning, and the ability to stop the campaign if vaccine efficacy is proving to be low, outweighs the perceived benefit of not vaccinating at all. In this scenario, if we were to implement this policy, it would result in 35 monitored vaccinations by day t^*. If at least 14 of these result in immunity, we would continue vaccination on day t^*, otherwise we would stop the campaign.

In summary, we observe that the three methods of incorporating the information

from monitored vaccinations result in different management decisions. The optimal policy for both a non-AM and passive AM approach is to forego vaccination for the entirety of the outbreak, since, under the prior distribution, the expected benefit of a full vaccination campaign is not sufficient to offset the cost of the vaccines. However, under active AM, we recognise that an ineffective campaign can be stopped on day t^*, saving the cost of administering the remaining vaccines and thus lowering the overall expected cost of immediate vaccination. Hence, the optimal policy for active AM is to start vaccination immediately and continue until the vaccine pool is depleted if monitored vaccinations are successful (in this scenario, if at least 14 of the 35 monitored vaccinations are successful), otherwise cease vaccination on day t^*. In this scenario, by incorporating the possible future results of monitored vaccinations into our initial decision, following active AM would reduce the expected cost of the outbreak by over 100 units (approximately 3%) compared to following a passive or non-AM approach. Hence, only active AM truly satisfies our management objective of minimising expected outbreak cost.

3.4 Scenario 2

In the second scenario we focus on our ability to minimise the duration of a theoretical epidemic ($\omega_1 = 1, \omega_2 = \omega_3 = \omega_4 = 0$; Section 3.2.2). Such an objective may be suitable for some livestock disease epidemics, for which eradicating the disease as quickly as possible is the primary concern, in order to minimise the impact on the economy through exports and tourism. We parameterise the epidemiological model using FMD-like parameters; transmission: $\beta = 0.2$, incubation: $\sigma = 0.2$ and removal/recovery: $\gamma = 0.1$, with $R_0 = 2$. Vaccination is limited to 100 individuals per day, with a total pool of 4500 vaccines. These are summarised in Table 3.1. Sensitivity to all these parameters is explored in detail in later sections.

As in scenario 1, there are a maximum of four possible campaigns that may be implemented by the end of the outbreak (Figure 3.4). Compared to scenario 1, the behaviour of the objective over the range of vaccine efficacy in this scenario is less intuitive. Here, if vaccine efficacy is low or too few vaccines are administered, we may see an increase in outbreak duration compared to taking no action. This occurs if the vaccination campaign is not sufficient to reduce the effective R_0 of the epidemic below 1 before it is stopped, leading to a longer, albeit much smaller, outbreak. Another consequence of this is that a delayed campaign (3: $\mathcal{V}_{t^*,t_{end}}$) can be more effective at shortening duration than an immediate campaign, since a delayed campaign allows the disease to spread unhindered for 7 days before vaccination is implemented, hence

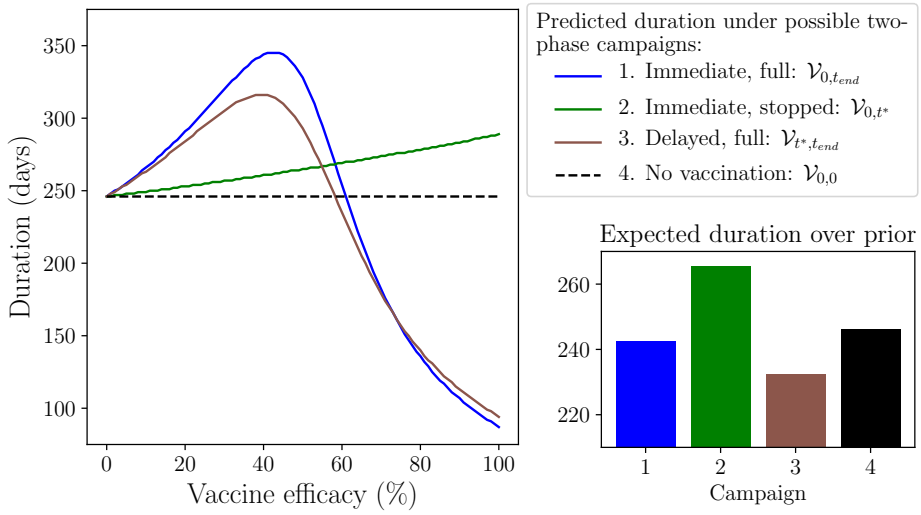


Figure 3.4: **Scenario 2: Predicted outbreak duration resulting from possible two-phase campaigns.** For the passive and active AM methods, the two decision points ($t = \{0, t^*\}$) result in four possible two-phase campaigns that may be implemented by the end of the outbreak: 1) vaccination is started immediately and continued until the vaccine pool is depleted, 2) vaccination is started immediately but stopped on day t^*, 3) vaccination is delayed until t^*, then continued until the vaccine pool is depleted, or 4) no vaccination is employed during the outbreak. The non-AM approach has only one decision point ($t = 0$), hence can only result in either campaign (1) or (4). Epidemiological and vaccination parameters are set to those in Table 3.1: Scenario 2. Expected duration is calculated over a $Beta(1.1, 1.1)$ prior distribution around vaccine efficacy.

the outbreak burns through the population faster. In scenario 1, when the number of infections was important not duration, a delayed campaign was never considered more effective than an immediate one.

Under the non-AM approach, we only compare campaigns (1: $\mathcal{V}_{0,t_{end}}$) and (4: $\mathcal{V}_{0,0}$): immediate, full vaccination or no vaccination respectively. The expected duration over the prior distribution around vaccine efficacy is lower for the former, hence the optimal policy for this approach is to vaccinate immediately and continue vaccination until the vaccine pool is depleted.

Under passive AM, an initial decision to vaccinate is assumed to always result in continued vaccination after day t^*, since stopping the campaign results in a higher expected duration over the prior distribution (Figure 3.4). Hence, the expected duration from an initial decision to vaccinate is equivalent to the expected duration from an immediate, full campaign (Figure 3.5 red line). In contrast to scenario 1, an initial decision not to vaccinate is assumed to result in vaccination from day t^*,

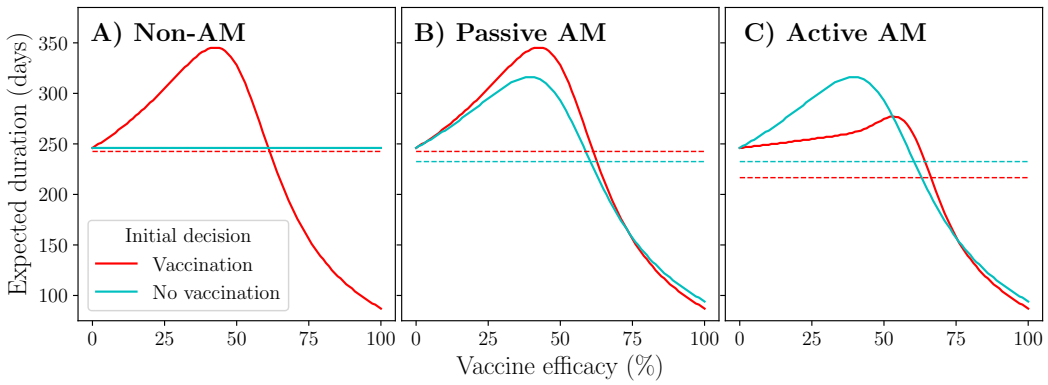


Figure 3.5: **Scenario 2: Expected outbreak duration resulting from an initial decision to vaccinate or not.** Expected outbreak duration from an initial decision to vaccinate (red) or not (blue), as viewed under non-AM (A), passive AM (B) and active AM (C) methods, conditional on the true value of efficacy. Dashed lines represent the expected duration calculated over a $Beta(1.1, 1.1)$ prior distribution around vaccine efficacy. Epidemiological and vaccination parameters are set to those in Table 3.1: Scenario 2.

hence leading to a delayed campaign ($\mathcal{V}_{t^*,t_{end}}$), since this provides a lower expected duration over the prior distribution than not vaccinating throughout the outbreak (Figure 3.4). Thus, in making the initial decision under passive AM, we compare the expected duration of an immediate, full campaign and a delayed campaign. In this case, the latter provides the lowest expected duration, as previously explained, hence the optimal policy for passive AM is to not vaccinate initially. Since our initial decision is not to vaccinate, no new information would be available on day t^*, hence the final decision would be to vaccinate from this day based on the prior distribution, leading to a delayed campaign.

Under active AM, we again recognise that an initial decision to vaccinate can lead to a final decision to continue vaccination, leading to campaign 1: $\mathcal{V}_{0,t_{end}}$, if the success rate of monitored vaccinations is sufficiently high, or stop vaccination, leading to campaign 2: $\mathcal{V}_{0,t^*}$, if the success rate is low. In this case, at efficacies below approximately 60%, it is more effective to stop vaccination on day t^* than continue it. Formally, in this scenario, an initial decision to vaccinate would lead to continued vaccination if there are at least 21 successes from the 35 monitored vaccinations, as this results in a posterior distribution around vaccine efficacy that assigns a lower expected duration to continuing than stopping. If there are less than 21 successful monitored vaccinations, we would stop vaccination on day t^*. Hence, the expected cost of an initial decision to vaccinate is a combination of campaigns (1) and (2) (Figure 3.5 red line). An initial decision not to vaccinate means there

are no monitored vaccinations to provide updated information regarding the vaccine efficacy, hence, as under the passive AM approach, the expected duration of such an initial decision is equivalent to that of a delayed campaign (Figure 3.5 blue line). For active AM, the optimal policy is to vaccinate initially, since it provides a lower expected duration over the prior distribution, again arising from the recognition that an ineffective campaign can be stopped on day t^*, reducing the negative effects of such a campaign.

Overall, as in scenario 1, we observe that the three methods of incorporating the information from monitored vaccinations result in different management decisions. Following a non-AM approach, the optimal policy is to vaccinate immediately and continue this until the vaccine pool is depleted. The optimal policy for passive AM is to not vaccinate immediately, but start vaccination on day t^* and continue until the vaccine pool is depleted. Finally, the optimal policy for active AM is to start vaccination immediately and continue until the vaccine pool is depleted if at least 21 of the 35 monitored vaccinations are successful, otherwise cease vaccination on day t^*. By incorporating the possible future results of monitored vaccinations into our initial decision, following an active AM approach leads to an expected duration that is almost 30 days shorter than if we followed a passive AM approach, a decrease of approximately 12%. Again, active AM is therefore the only approach that truly meets our objective to minimise the expected outbreak duration.

3.5 Sensitivity

In the following sections, we perform sensitivity analyses on the parameters within the model that we have fixed. These include the definition of prior information, amount of real-time information gathered through monitoring, restrictions on control, relative costs and the value of epidemiological parameters.

3.5.1 Prior information

Thus far, in both scenarios, we have assumed a very low level of prior information regarding the efficacy of the vaccine, defined by a $Beta(1.1, 1.1)$ distribution (Section 3.2.3). If we increase the amount of prior information available, in either scenario, it becomes more likely that the approaches will make the same initial decision, since the information gained from monitored vaccinations has relatively less impact. Which choice is made, to vaccinate initially or not, depends on the estimate of efficacy that is suggested by the prior information (the mode of the distribution $\frac{x_0}{x_0+y_0}$) and the

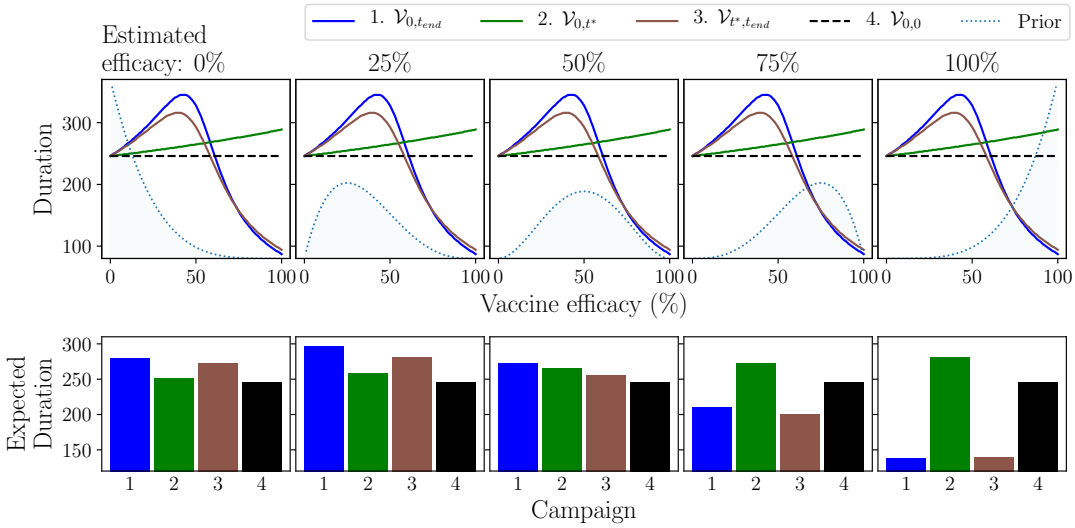


Figure 3.6: **Example effect of prior information on the expected duration of the outbreak under each campaign.** The expected duration of the outbreak under each campaign is calculated over the prior distribution around vaccine efficacy, defined by a $Beta(x_0 + 1, y_0 + 1)$ distribution (Methods: Prior and real-time information). We set $x_0 + y_0 = 4$ and vary the estimate of vaccine efficacy (the mode of the distribution $\frac{x_0}{x_0+y_0}$) across columns. Row 1: visual representation of how the prior distribution changes with estimated efficacy. Row 2: expected duration of the outbreak under each campaign for different estimates of vaccine efficacy. Epidemiological and vaccination parameters are set to those in Table 3.1: Scenario 2.

amount of information supporting this estimate, or concentration, $(x_0 + y_0)$. In this section, we focus on the effect of changing the prior information under scenario 2 (Figures 3.6 - 3.9), however similar conclusions can be drawn from scenario 1, for which the results are provided in Appendix A (Figures A.1 - A.3).

Changing the prior distribution affects the expected duration of all vaccination campaigns, except the 'no vaccination' campaign (Figure 3.6). This in turn affects the expected outcome of both an initial decision to vaccinate and an initial decision to not vaccinate, for all approaches (Figure 3.7).

If the estimate of efficacy provided by the prior information (columns in Figures 3.6 and 3.7, x-axis in Figure 3.8) is low, more weight is given to the predicted duration at low efficacies, hence foregoing vaccination entirely becomes the optimal campaign. If there is enough information supporting this estimate, an initial decision not to vaccinate is chosen by all approaches and, since there are no vaccinations to monitor, the choice not to vaccinate will continue throughout the outbreak. The amount of information required for this to occur depends on the approach used (Figure 3.8). Under passive AM, even with no prior information (a flat prior distribution over

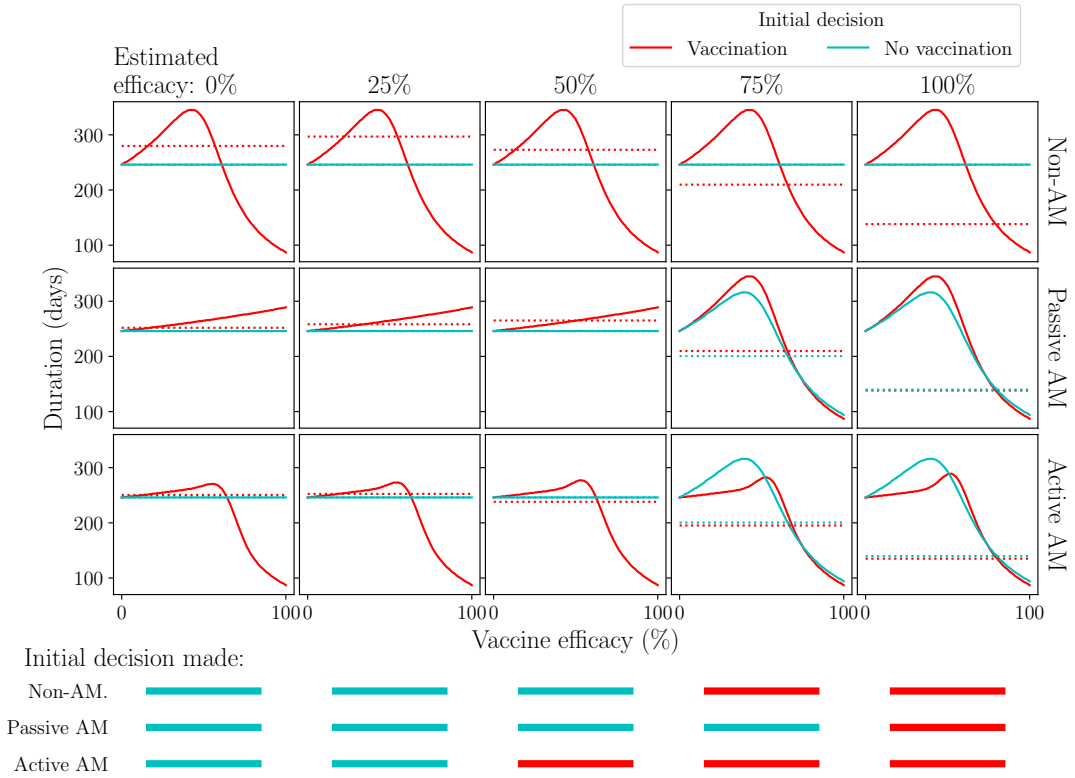


Figure 3.7: **Example effect of prior information on the expected duration of the outbreak given an initial decision to vaccinate or not.** We set $x_0 + y_0 = 4$ and vary the estimate of vaccine efficacy (the mode of the distribution $\frac{x_0}{x_0+y_0}$) across columns. Rows 1-3: predicted outbreak duration over vaccine efficacy, given an initial decision to vaccinate (red) or not (blue), for different prior estimates of efficacy, as viewed under a non-AM, passive AM or active AM approach respectively. Bottom row: initial decision made under each approach, for different prior estimates of efficacy: vaccinate (red) or don't (blue). Epidemiological and vaccination parameters are set to those in Table 3.1: Scenario 2.

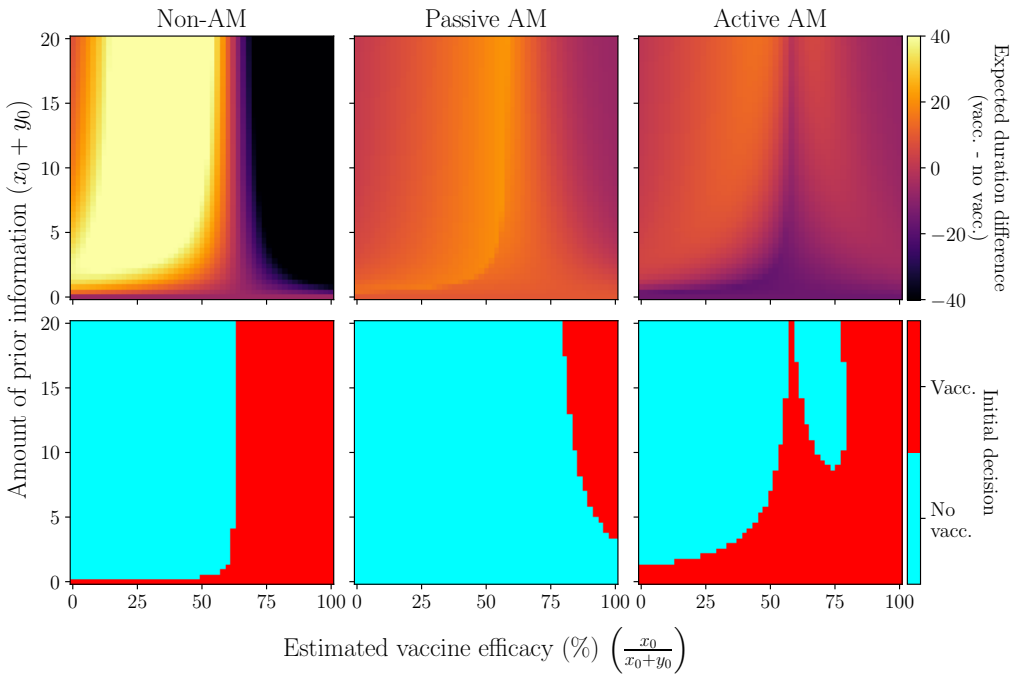


Figure 3.8: **Scenario 2: Initial decision made under each approach given different prior information.** We define prior information using a Beta(x_0+1, y_0+1) distribution and vary the estimated efficacy (the mode of the distribution; $\frac{x_0}{x_0+y_0}$) and the amount of information supporting this estimate ($x_0 + y_0$). Top row: difference in expected duration between vaccinating initially or not, as viewed under each approach. Bottom row: initial decision made under each approach: vaccinate (red) or not (blue). Epidemiological and vaccination parameters are set to those in Table 3.1: Scenario 2.

vaccine efficacy) we would choose not to vaccinate. Under a non-AM approach, we require only a very small amount of prior information suggesting efficacy is low to switch from vaccinating to not vaccinating. Finally, under active AM we require slightly more information supporting a low estimate of efficacy ($x_0 + y_0 > 2$) to make the same switch, since it recognises the possibility that monitored vaccinations may reveal the vaccine efficacy to be higher than estimated.

As the prior estimate of vaccine efficacy increases, more weight is given to the predicted duration of the campaigns at higher efficacies, hence both the immediate, full (1: $\mathcal{V}_{0,t_{end}}$) and delayed (3: $\mathcal{V}_{t^*,t_{end}}$) campaigns become more effective under the prior distribution (Figure 3.6). As a result, the expected duration from an initial decision not to vaccinate switches from being based on no vaccination to delayed vaccination for both passive and active AM (Figure 3.7). Since an immediate, full vaccination campaign only results in a shorter outbreak for very high vaccine efficacies ($>\sim 80\%$), compared to a delayed campaign, under passive AM we require a significant amount of prior information supporting an estimate this high to change our

initial decision (Figure 3.8). Under active AM, however, at low efficacies the shorter predicted duration resulting from vaccinating until day t^* and stopping if monitored vaccinations are unsuccessful (campaign 2: $\mathcal{V}_{0,t^*}$), compared to a delayed campaign that must continue until all vaccines are used, allows the expected duration of an initial decision to vaccinate remain lower than not vaccinating. If vaccine efficacy is very high ($>\sim 80\%$) an immediate, full campaign is optimal, hence estimates in this range also result in an initial decision to vaccinate. Only if there is strong prior information supporting an estimate of efficacy between approximately 55% and 75% will we opt not to vaccinate initially under active AM, since between these values a delayed campaign is optimal (Figure 3.4).

The degree of agreement between passive and active AM depends heavily on the prior estimate of efficacy and the strength of information supporting this estimate (right-hand panel; Figure 3.9). For any estimate of efficacy, we require at least $x_0 + y_0 > 2$ for the approaches to agree. This equates to having the amount of information that two monitored vaccinations would provide, prior to the outbreak beginning. For some estimates, such as around 55% and 80%, we require a very large amount of prior information ($x_0 + y_0 > 20$) for the approaches to agree, since, at these points, the rank of the campaigns cross over causing uncertainty as to which choice is truly optimal. This can result in significantly different expected durations between the two approaches, especially for estimates around 55% where there is still a relatively high possibility that efficacy is low enough to extend the outbreak duration (left-hand panel; Figure 3.9). However, for estimates around 80%, whilst the approaches may differ in initial decision, the expected durations under both are similar, since if vaccine efficacy is high there is only a small difference implementing an immediate, full campaign (1: $\mathcal{V}_{0,t_{end}}$) under active AM and a delayed campaign (3: $\mathcal{V}_{t^*,t_{end}}$) under passive AM. Hence, a different initial decision does not necessarily lead to a significantly different outcome in terms of the management objective.

Finally, we note that our definition of prior information and requirement that $x_0, y_0 \geq 0$, allows for at most one mode (or none, in the case of a uniform prior). This excludes distributions with two modes, at 0 and 1, that would result if we allowed $-1 \leq x_0, y_0 \leq 0$. Whilst a polarised belief around vaccine efficacy would be uncommon, it could easily be incorporated into this framework. In this scenario, where $\nu_e = 0$ results in the outcome of all campaigns converging, the mode at $\nu_e = 1$ would dominate and immediate, full vaccination would be the obvious choice under all management approaches. In scenario 1 (Figures A.1 - A.3), the campaigns diverge at both extreme values of vaccine efficacy, vary almost linearly between and switch rank at close to 50% efficacy. Hence, our decisions would be very similar to those we

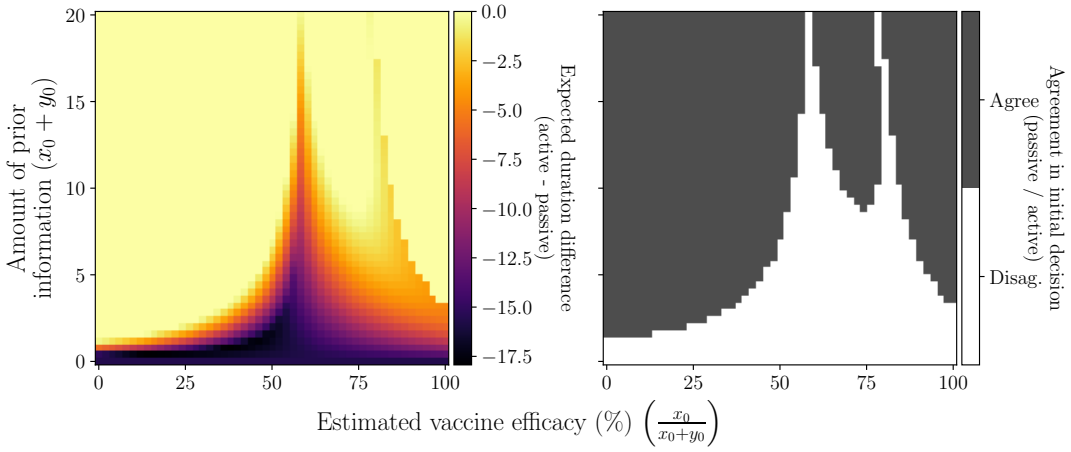


Figure 3.9: **Scenario 2: Comparison of initial decision made between active and passive AM given different prior information.** We define prior information using a Beta$(x_0 + 1, y_0 + 1)$ distribution and vary the estimated efficacy (the mode of the distribution; $\frac{x_0}{x_0+y_0}$) and the concentration $(x_0 + y_0)$. Left panel: difference in expected duration under active AM compared to passive AM. Right panel: agreement in initial decision between passive AM and active AM. Epidemiological and vaccination parameters are set to those in Table 3.1: Scenario 2.

obtain under a unimodal distribution, following whichever mode carries the most weight.

Overall, we find that as long as there is still significant uncertainty as to which choice of initial action is best, even with prior information, active AM will result in a lower expected cost than passive AM and is hence the only approach that truly minimises the expected duration of the outbreak given the information and resources available.

3.5.2 Monitoring

For active AM, the initial control decision depends on the number of vaccinations that are monitored for success. This occurs through the expected outcome given an initial decision to vaccinate ($E[C(a_0 = vac)]$; Equation 3.11), which will depend on how the outcomes of monitored vaccinations affect the posterior distribution around vaccine efficacy (the expected outcome given an initial decision not to vaccinate does not depend on the number of monitored vaccinations since it does not allow monitoring). We explain in detail this effect for scenario 2 (Figure 3.10); however analogous statements can easily be made for scenario 1 (Figure A.4).

First, if no monitoring is planned, active AM views an initial decision to vaccinate

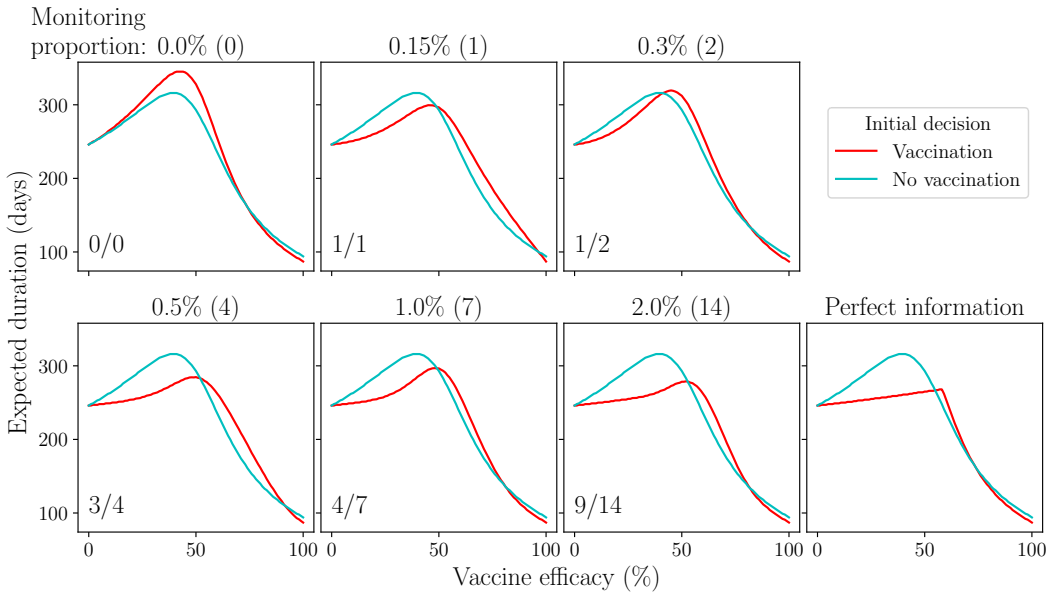


Figure 3.10: **Scenario 2: effect of monitoring proportion on the predicted outbreak duration given an initial decision to vaccinate or not.** Predicted outbreak duration over vaccine efficacy, given an initial decision to vaccinate (red) or not (blue), for different monitoring proportions (ρ; Table 3.1). The number of monitored vaccinations is given in brackets beside the proportion. The required number of successful vaccinations from the total number monitored in order to make a decision to vaccinate is shown in the lower left corner of each panel. The far right panel assumes perfect information is obtained after day t^*, that is, we will know the true vaccine efficacy exactly when making the final decision. Epidemiological and vaccination parameters are set to those in Table 3.1: Scenario 2.

in the same way as passive AM, hence assumes that the campaign will always be continued until all vaccines are used since this produces a lower expected duration than stopping the campaign on day t^* over the prior distribution around vaccine efficacy. Thus, the expected duration from an initial decision to vaccinate converges to that of an immediate, full campaign at low monitoring proportions (top-left; Figure 3.10). In this case, we would make an initial decision not to vaccinate, with the intention of vaccinating from day t^* instead, as under passive AM.

As the amount of monitoring increases, the expected duration from an initial decision to vaccinate diverges from that of an immediate, full campaign, becoming a weighted combination of both an immediate, full campaign ($\mathcal{V}_{0,t_{end}}$) and a campaign that is stopped on day t^* ($\mathcal{V}_{0,t^*}$; Figure 3.10). This is the result of having monitored vaccinations to inform the final decision: if successes are low, stop the campaign, otherwise continue it. If we have only one monitored trial, we require it to be successful to continue the campaign. Even at low values of vaccine efficacy, there is still a chance that the monitored vaccination will be successful, hence the campaign may be continued when it should not be. The opposite is true at high values of efficacy. As a result, the predicted duration does not coincide exactly to either of the two campaigns that we can choose from, but rather a weighted average of the two. With two monitored vaccinations, we require only one of the two to be successful to continue the campaign. As the number of monitored vaccinations continues to increase, the required number of successes approaches 60% of the total, as this is the value of efficacy at which continuing the campaign becomes more effective than stopping it.

With more trials, the probability of making an incorrect final decision falls. That is, there is less chance of achieving higher than 60% successes if the true vaccine efficacy is actually below this, and vice versa. As a result, the predicted duration from an initial decision to vaccinate more closely approximates a stopped campaign ($\mathcal{V}_{0,t^*}$) at low efficacies and a full campaign ($\mathcal{V}_{0,t_{end}}$) at high efficacies. Only at efficacy values close to 60% do we still see a significant divergence from both. If we were to assume that monitoring provided perfect information (as in the calculation of EVPI; Section 2.2), we assume that we always make the correct final decision. This is equivalent to the posterior distribution of vaccine efficacy being a single point at the true value and results in a predicted duration from an initial decision to vaccinate coinciding exactly with either the immediate, full campaign or stopped campaign, with no divergence even when close to the true efficacy (bottom-right; Figure 3.10). We explore this idea further in the next chapter.

Overall, the effect of having more monitoring information reduces the probability

of making an incorrect final decision. For both scenarios, this will lower the expected cost or duration from an initial decision to vaccinate towards that provided by perfect information (Figure 3.11). We require only one monitored vaccination for learning about vaccine efficacy to make an initial decision to vaccinate the optimal decision. We also see that, whilst we can always allocate more resources to monitoring to lower the expected outcome towards that provided by perfect information, the effect of doing so decreases and becomes negligible after approximately 70 monitored vaccinations ($\rho = 10\%$). If we were to assign a cost to monitoring itself, there would be a point at which adding more monitoring would cost more than it was worth, leading to a single minima which active AM can be used to find (right-hand column; Figure 3.11). For scenario 1, a cost per monitored vaccination equivalent to 25% of the cost of an infection results in an optimal monitoring proportion of 5%. Similarly, for scenario 2, a cost per monitored vaccination equivalent to 10% of the daily cost of the outbreak results in an optimal monitoring proportion of 5%. As the cost of monitoring increases, the optimal monitoring proportion will clearly fall and the best attainable outcome (expected cost or duration) will rise (Figure 3.12). If the monitoring cost is high enough, an initial decision to vaccinate may no longer be optimal.

3.5.3 Restrictions on control

The vaccination campaigns are defined by a fixed daily vaccination rate (ν_r), finite vaccine pool (ν_{pool}) and a single day on which real-time information can be used to adapt control (t^*). In both scenarios, these conditions have so far been fixed (Table 3.1); however they have a significant effect on the decisions made by our approaches, causing the outcomes to be trivial in some cases and complex in others (Figures 3.13 and 3.14).

First, we vary the vaccine pool and keep the other two control restrictions constant (1st column; Figures 3.13 and 3.14). In both scenarios, if the vaccine pool is too small, we will choose to forego vaccination for the entirety of the outbreak. In scenario 1, this is due to the cost of implementing the vaccination campaign outweighing the number of infections avoided, and in scenario 2, because administering such a small number of vaccines is likely to increase the duration of the outbreak even with a highly effective vaccine (Figure A.5). In scenario 1, we see that a very large vaccine pool ($\nu_{pool} > 3200$) will also cause us to forego vaccination, since the relative effect of each vaccine, in terms of the reduction in the number of infections each causes, is diminished so much that the campaign is no longer cost effective (Figure A.5). However, if the vaccine pool is neither too small nor too large to make the initial

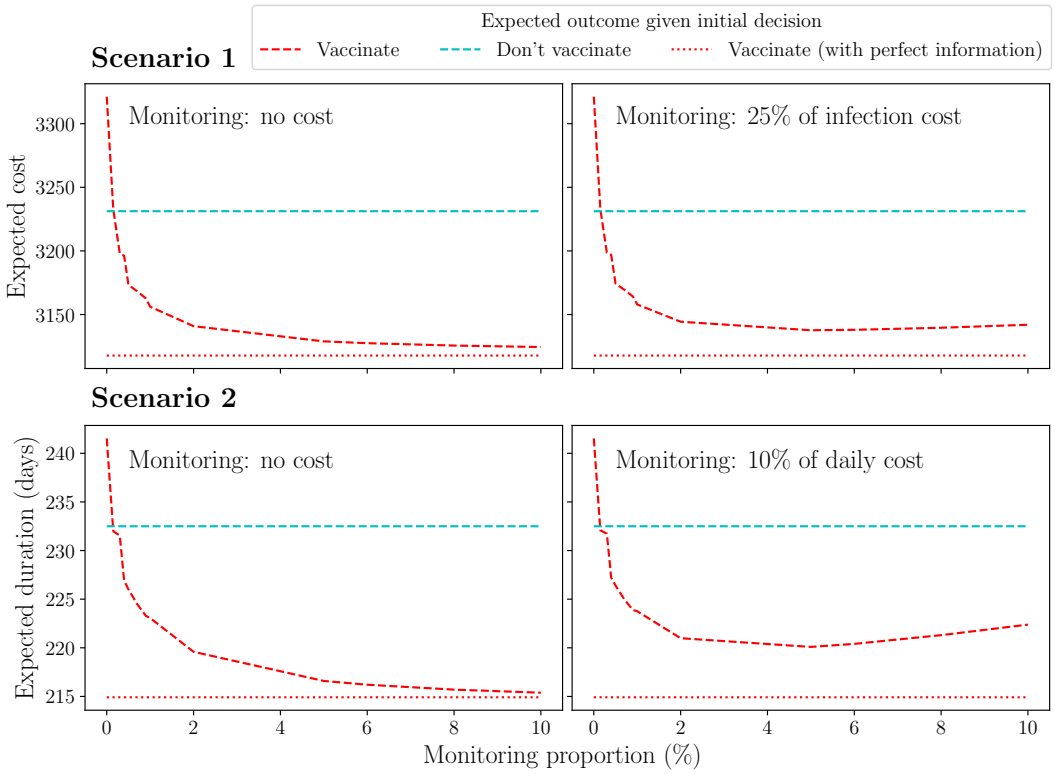


Figure 3.11: **Effect of monitoring proportion on the expected cost/duration given an initial decision to vaccinate or not.** Top row: expected cost (scenario 1) given an initial decision to vaccinate (red) or not (blue) for a range of monitoring proportions, with and without a cost associated with monitoring (right and left panel respectively). '25% of infection cost' refers to the cost assigned to monitoring a single vaccination, relative to the cost of a single infection. Bottom row: same as top row for scenario 2. The dotted red line represents the expected cost/duration given an initial decision to vaccinate, assuming monitored vaccinations provide perfect information after day t^*.

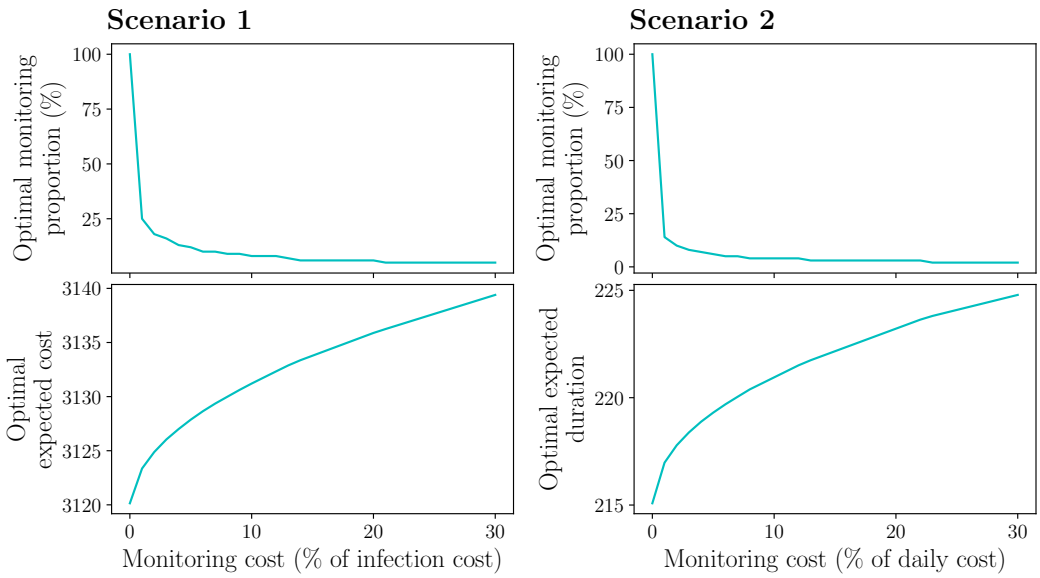


Figure 3.12: **Effect of cost associated with monitoring on the optimal monitoring proportion and optimal expected cost/duration given an initial decision to vaccinate.** Top row: optimal monitoring proportion given an initial decision to vaccinate for a range of monitoring costs, for scenario 1 (left) and scenario 2 (right). Bottom row: optimal expected outcome (cost or duration) given an initial decision to vaccinate for a range of monitoring costs.

decision obvious, our approaches will lead to different decisions. Furthermore, we note that, if we were not to fix the vaccine pool, but rather try to optimise its size, only active AM could be relied on to do so. This is clear in the case of scenario 1: active AM can clearly identify that a vaccine pool size of 2500 leads to the lowest expected cost from the outbreak, since it minimises the expected cost of an initial decision to vaccinate (1st column; Figure 3.13). However, both passive and non-AM would suggest that 2000 vaccines is the optimal pool size, if they were to vaccinate, since they are biased by the high cost of an ineffective campaign, which is avoided under active AM since we recognise that an ineffective campaign can be stopped before the vaccine pool is depleted.

Next, we vary the daily vaccination rate, keeping the vaccine pool size and t^* constant (2nd column; Figures 3.13 and 3.14). For both scenarios, a high daily rate highlights no vaccination as the obvious choice, although for slightly different reasons. In scenario 1, a high daily rate improves the effectiveness of all vaccination campaigns, however the benefit of being able to stop a campaign that is ineffective is removed, hence we can no longer exploit this through active AM (Figure A.6). In contrast, in scenario 2, a higher daily rate worsens our campaigns, since the negative effects of vaccination (increased duration at low vaccine efficacy) are exaggerated.

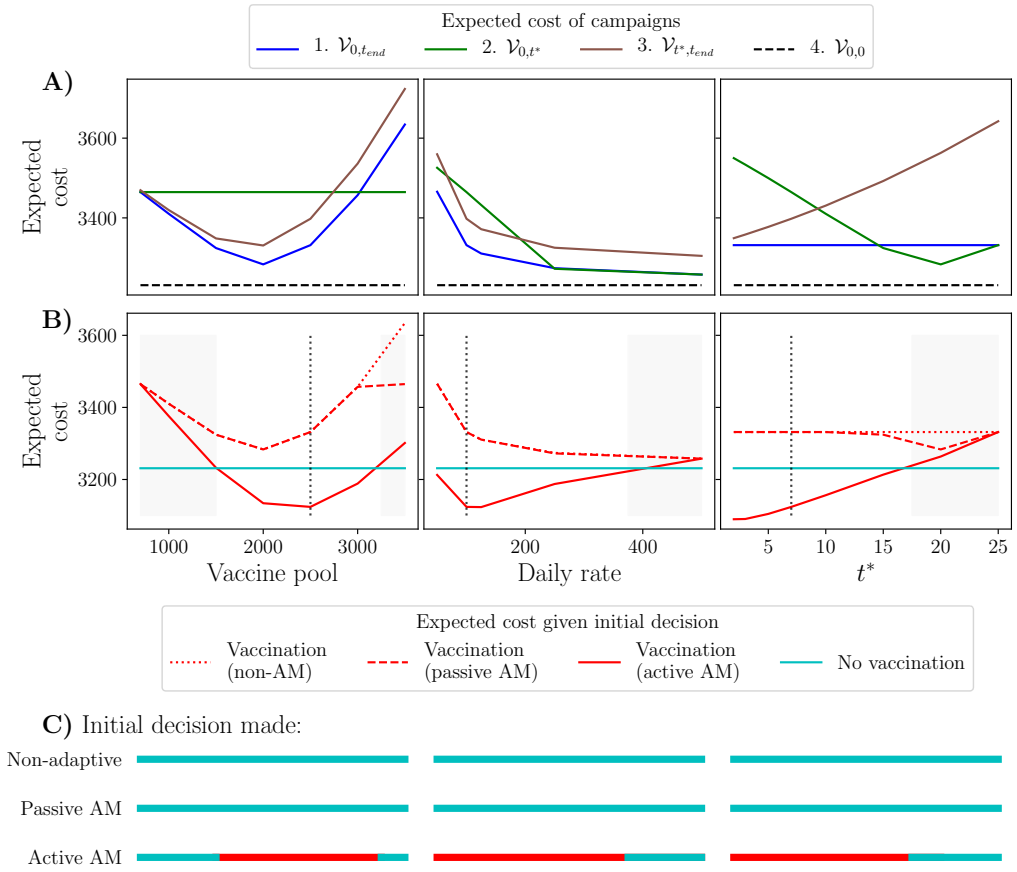


Figure 3.13: **Sensitivity of scenario 1 results to restrictions on control.** Varying the vaccine pool (ν_{pool}), daily vaccination rate (ν_r) and length of the monitoring period (t^*), we display the change in expected cost given both the campaigns (row A) and initial decision under each approach (row B). Row C displays the initial decision made under each approach for different values of these parameters. Parameters a varied one at a time, keeping all others constant at the values provided in Table 3.1. Vertical dotted lines identify the default parameter values used throughout. Areas of the parameter space for which passive and active AM agree in their initial decisions are shaded grey.

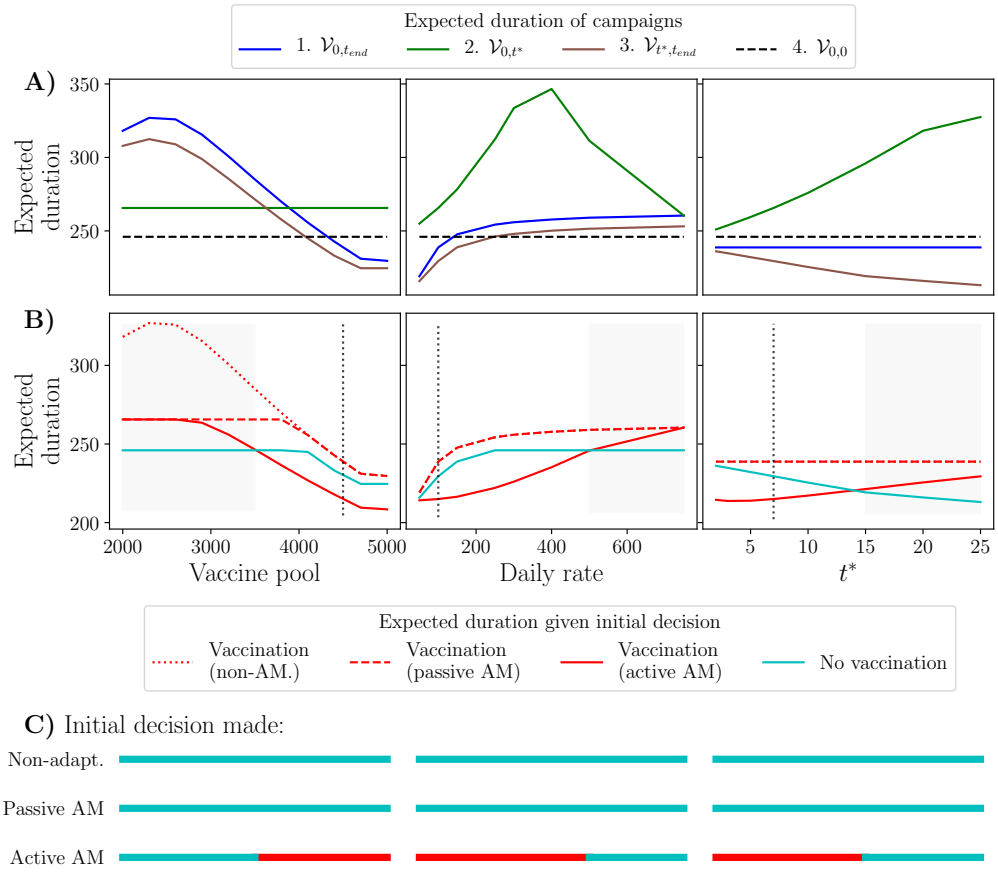


Figure 3.14: **Sensitivity of scenario 2 results to restrictions on control.** Varying the vaccine pool (ν_{pool}), daily vaccination rate (ν_r) and length of the monitoring period (t^*), we display the change in expected duration given both the campaigns (row A) and initial decision under each approach (row B). Row C displays the initial decision made under each approach for different values of these parameters. Parameters a varied one at a time, keeping all others constant at the values provided in Table 3.1. Vertical dotted lines identify the default parameter values used throughout. Areas of the parameter space for which passive and active AM agree in their initial decisions are shaded grey.

Alongside this, the benefit of stopping an ineffective campaign under active AM is again reduced, hence the obvious decision becomes to not vaccinate (Figure A.6). However, if the daily vaccination rate is not too large (scenario 1: < 400, scenario 2: < 500), the approaches will lead to different initial decisions. Again, we note that if we wanted to optimise the daily rate rather than assume it fixed, active AM is the only approach that can do so. This is highlighted in scenario 1: under active AM we identify a daily rate of approximately 100 per day as the optimal (2nd column; Figure 3.13), allowing learning about vaccine efficacy without committing too many vaccines early on. However, under a non-AM or passive AM approach we would opt to vaccinate as quickly as possible.

Finally, we vary the day on which we use the results from monitored vaccinations to adapt control (t^*), keeping the vaccine pool size and daily rate constant (3rd column; Figures 3.13 and 3.14). For both scenarios, if this day is too far in the future, an initial decision not to vaccinate becomes the obvious optimal choice. For scenario 1, this will lead to a final decision also not to vaccinate, caused by the fact that the benefit of stopping an ineffective campaign is removed (as with a highly daily vaccination rate), since most of the vaccine pool will have already been used. In scenario 2, the benefit of stopping an ineffective campaign is also removed, but the effectiveness of a delayed campaign is also increased due to a longer delay (Figure A). As a result, in this scenario high values of t^* lead to the implementation of a delayed campaign under both adaptive approaches, and an immediate, full campaign under a non-AM approach. If we wished to optimise the length of this delay in scenario 2, under a passive AM approach we would choose to make it as long as possible, to optimise a delayed campaign, whereas under active AM we could identify a better optimal for values of t^* around 5 days (3rd column; Figure 3.14).

3.5.4 Management objective

It is clear from the contrast between scenarios 1 and 2 that the management objective has a significant impact on the decisions made under any of the three approaches. Furthermore, in scenario 1, the relative costs of infections compared to vaccinations will also have such an influence. If the costs of vaccination (both per vaccine costs, ω_3, and a fixed cost associated with implementing a vaccination campaign, ω_4) are sufficiently high, an initial decision to vaccinate will not be deemed optimal under any approach. Similarly, if these vaccination costs are sufficiently low, vaccination becomes the obvious choice and we will choose to vaccinate under all approaches. However, there is a region in which the choice is not so obvious, where the costs of vaccination may be outweighed by the reduction in infections if the vaccine is

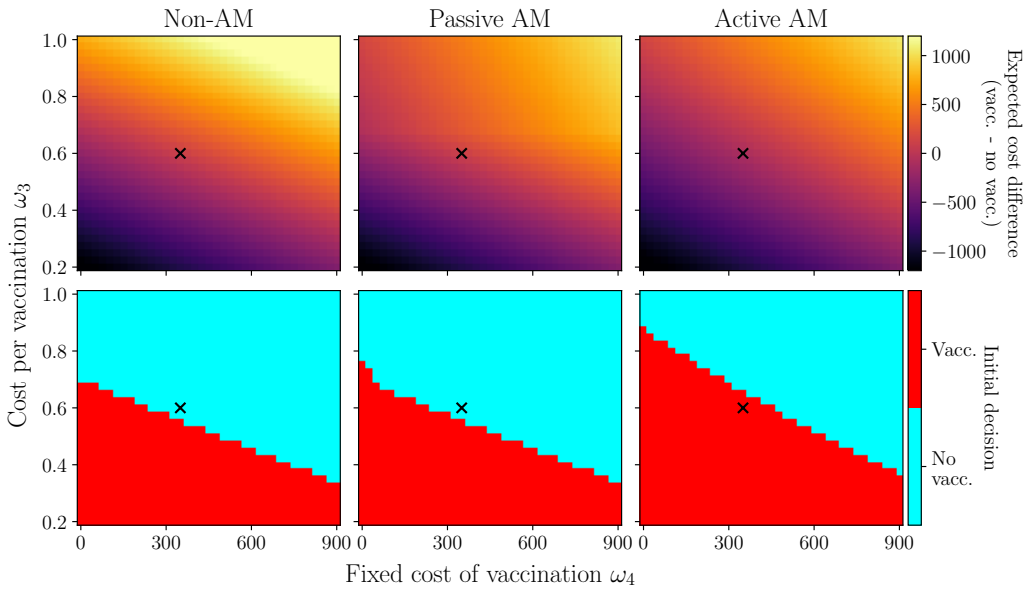


Figure 3.15: **Scenario 1: initial decisions given different relative costs associated with vaccinations and infections.** We vary the cost per vaccination (ω_3) and fixed cost associated with implementing a campaign (ω_4), relative to the cost per infection ($\omega_2 = 1$). Top row: difference in expected cost between an initial decision to vaccinate or not, as viewed under each approach. Bottom row: initial decision made under each approach. Black crosses represent the default values used in scenario 1 (Table 3.1).

effective, but may not if it is ineffective. It is in this region that the initial decision differs between approaches: under active AM we choose to vaccinate and thereby learn about the vaccine efficacy, allowing greater reduction in infections if vaccine efficacy is high, but under the non-AM or passive AM approaches we are unable to foresee the greater worth of doing this and therefore choose not to vaccinate at all. The difference in cost resulting from these decisions depends on the specific definition of relative costs (Figure 3.16), however is most pronounced for lower vaccine costs, where the benefit of vaccinating is emphasised.

3.5.5 Epidemiological parameters

The dynamics of the epidemic itself can also render the decision making problem trivial or highly complex. For example, in scenario 1, if R_0 is less than 1, the epidemic will die out very quickly by itself and hence it is clearly not worth incurring the cost of implementing a vaccination campaign, so under all approaches we would choose not to vaccinate. However, if $R_0 > 1$, we see that only under active AM do we choose to vaccinate (Figure A.7).

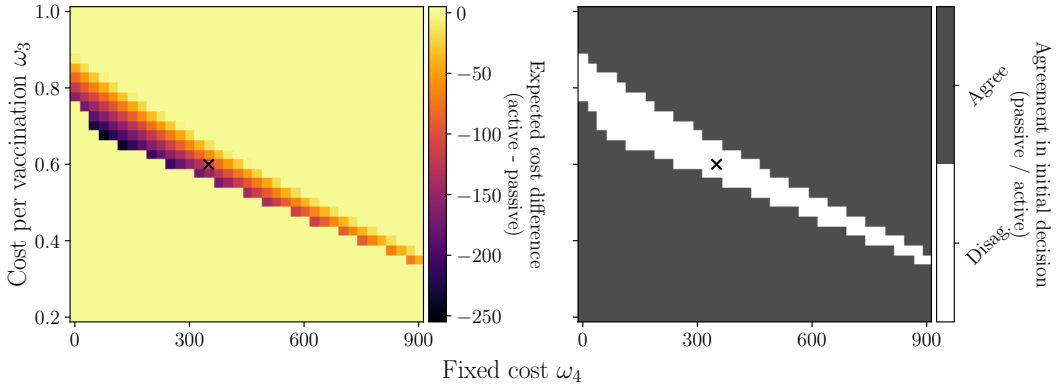


Figure 3.16: **Scenario 1: initial decisions given different relative costs associated with vaccinations and infections.** We vary the cost per vaccination (ω_3) and fixed cost associated with implementing a campaign (ω_4), relative to the cost per infection ($\omega_2 = 1$). Left panel: difference in expected cost under active AM compared to passive AM. Right panel: agreement in initial decision between passive AM and active AM. Black crosses represent the default values used in scenario 2 (Table 3.1).

We see a similar, but more complex, relationship in scenario 2. If R_0 is very low ($R_0 < 1$) or high ($R_0 > 8$), the negative effects of vaccination (increased duration at low vaccine efficacy) are diminished and hence we would choose to vaccinate under any approach (Figures 3.17 and 3.18). However, between these values, our decision depends on the approach we take. This is most pronounced for $1 < R_0 < 4$, with slow recovery rates from infection (long infectious periods). In such circumstances, under passive AM the apparent benefit of a delayed vaccination campaign (under the prior distribution) causes us to make an initial decision not to vaccinate, however this removes our ability to learn. The long infectious period results in an exaggerated negative impact if vaccine efficacy is in fact low. Under active AM however, we recognise this and make an initial decision to vaccinate and learn about efficacy, allowing us to avoid the significant negative impacts of an ineffective vaccine. For epidemics with higher transmission rates and shorter infectious periods, the benefit of a delayed campaign may outweigh the benefit of learning and stopping an ineffective campaign (Figure A.9).

In reality we will often be dealing with epidemics with an R_0 in this range, for example Ebola, flu, cholera, plague, Zika, to name a few. Only rarely will a disease have an R_0 value significantly higher than this, such as measles, and if the R_0 is below 1 then it is unlikely to cause a significant outbreak requiring complex control recommendations.

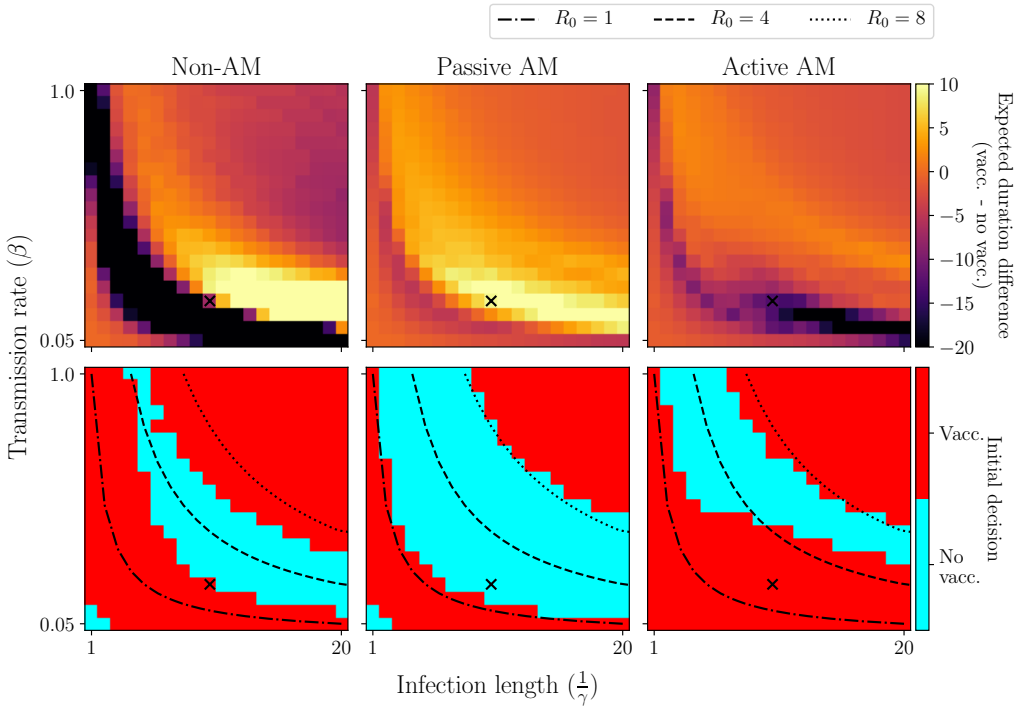


Figure 3.17: **Scenario 2: Initial decision made under each approach, varying epidemiological parameters.** We vary the epidemiological parameters describing transmission (β) and recovery/removal (γ). Top row: difference in expected duration between vaccinating initially or not, as viewed under each approach. Bottom row: initial decision made under each approach: vaccinate (red) or not (blue). Black crosses represent the default values used in scenario 2 (Table 3.1). Lines of constant R_0 are identified with black lines.

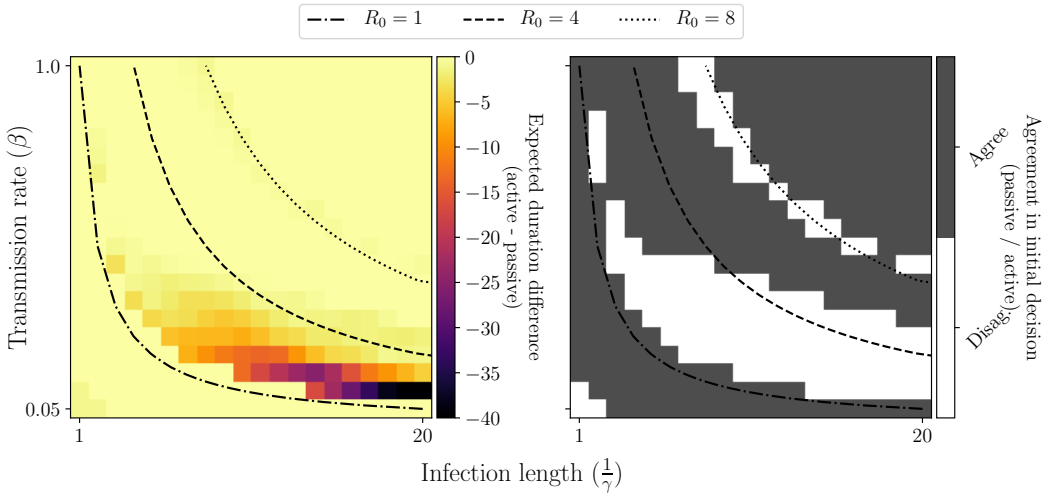


Figure 3.18: **Scenario 2: Comparison of initial decision made between active and passive AM given different epidemiological parameters.** We vary the epidemiological parameters describing transmission (β) and recovery/removal (γ). Left panel: difference in expected duration under active AM compared to passive AM. Right panel: agreement in initial decision between passive AM and active AM. Black crosses represent the default values used in scenario 2 (Table 3.1). Lines of constant R_0 are identified with black lines.

3.6 Conclusions and discussion

In this chapter we have developed a model to investigate the effectiveness of adaptive management strategies to control outbreaks of infectious diseases, following different approaches to incorporating real-time information regarding the unknown efficacy of a vaccine. Such approaches may be necessary in the context of infectious disease outbreaks, in which resources are limited, so must be used strategically (e.g. [29, 30, 104]), and the effectiveness of any vaccination campaign at the start of an outbreak may be uncertain (e.g. [138]).

We have found that, not only the ability to adapt control in light of new information, but also the ability to foresee such adaptation, can have a significant effect on the recommendations made and the outcome of the epidemic. Both passive and active AM can improve on a non-AM approach by more appropriately timing the introduction of control or stopping an ineffective campaign when necessary. In a two-phase control set-up such as this, should passive and active AM make the same initial decision, they will result in the same outcome. However, because of the way in which they view an immediate campaign under uncertainty, their initial decisions may differ. In both scenarios we analysed, under active AM, the ability to foresee

the option of stopping an ineffective campaign if monitored vaccinations are proving unsuccessful significantly lowered the expected cost (or duration) that would result from an initial decision to vaccinate, when compared with passive AM. This led to an initial decision to vaccinate under active AM, whilst under passive AM we would opt not to vaccinate from the start of the outbreak, removing our ability to learn about vaccine efficacy and ultimately increasing the expected cost (duration) of the outbreak. Therefore, under active AM we are better able to meet the objectives of management. This remained the case across all sensitivity analyses, in which active AM was always at least as good, often better, at meeting management objectives as the other two approaches. We emphasise here that active AM does not necessarily enforce experimentation of control, but provides a mechanism to assess the benefit of such an approach and implement it if it will lead to better outcomes in the future.

Although the main result in both scenarios led to contrasting recommendations between passive and active AM, this is highly dependent on the parameters used. Under certain conditions, the uncertainty around vaccine efficacy does not translate into uncertainty regarding control preference. If taking no action becomes the obvious choice, then all approaches will make the same decision not to vaccinate. This is found to occur if the vaccine pool is too small for a campaign to have a significantly positive effect, or similarly if the daily vaccination rate is too high, monitoring period too long, or vaccines too expensive. Conversely, immediate, full vaccination may also become the obvious choice if the cost of vaccines is very low compared to the cost of an infection (for scenario 1), or if the R_0 of the outbreak is very low or high (for scenario 2). It is plausible that, from a public relations point of view, the cost of appearing not to be taking every possible action to curb an outbreak would be considered high enough that not vaccinating initially would never be an option. However, this highlights another of the benefits of active AM: it provides a complete, evidence based plan of action for all stages of the outbreak, clearly outlining control recommendations conditional on different monitoring outcomes and the effect each will have on our ability to satisfy management objectives. Access to this information makes it easier to justify tough, and possibly unintuitive, decisions at early stages of the outbreak, if those decisions are shown to significantly improve the outcome of control in the future. Such scenarios are often not obvious from the outset, hence, whilst an active AM approach may not result in a different recommendation to less complex approaches, this cannot be known *a priori*. Therefore, active AM is useful even if just to confirm and provide evidence supporting the obvious choice of action.

The prior information regarding vaccine efficacy also has a significant effect on the recommendations made by each approach and the difference between them.

As the amount of prior information increases, the relative importance of real-time information is reduced, hence we expect the difference between passive and active AM to be less. Intuitively, if prior information suggests efficacy is low, the approaches are more likely to choose not to vaccinate, whereas if the estimate of efficacy is high, the approaches are more likely to choose to vaccinate. However, if the prior information still leaves uncertainty as to which campaign is optimal, due to a lack of information or the estimate of efficacy being close to where campaigns switch rank, we are likely to see a difference in recommendations between the approaches.

Care should be taken when using prior information alongside real-time information, since, if given too much weight (i.e. the variance of the prior distribution is disproportionately low), it can render the latter redundant. If prior information has been taken from previous outbreaks, it may be inaccurate and hence lead to suboptimal management. For example, in scenario 2, if prior information suggests that vaccine efficacy is between 60-80%, but it is actually significantly lower, relying heavily on this information may lead to opting for a delayed campaign under both active and passive AM, when not vaccinating is truly optimal. This would cause a significant increase in the duration of the outbreak. However, if we reduce the weight we place on prior information, active AM is able to recognise that the true efficacy may still be low and hence chooses to vaccinate immediately, reduce uncertainty and stop the campaign if vaccine efficacy is proving to be lower than expected, thereby avoiding much of the negative impact of an ineffective campaign. Thus, active AM allows us to lessen our reliance on prior information.

Under active AM, it is also possible to provide more relevant information to decision-makers regarding the amount of monitoring required and the timing and delivery of the vaccines. If there is a cost associated with monitoring, as we would expect in reality, active AM is able to identify the point at which monitoring no longer provides enough information regarding vaccine efficacy to offset the cost of that monitoring. This helps to avoid wasting resources on monitoring that will not affect the control recommendations, possibly allowing more resources to be allocated to control itself. Similarly, under active AM we can optimise the delivery of control through the vaccine pool size, daily vaccination rate and length of the monitoring period, with state-dependent recommendations providing a plan for control from start to finish. This is not possible under the other approaches. The use of active AM to optimise the delivery of control and monitoring resources is explored further in the next chapter.

In this chapter we have focused upon a relatively simple non-spatial model, with non-specific parameters chosen to mirror common non-fatal, human and livestock

diseases. We have additionally only focused upon a single uncertainty upon vaccine efficacy to highlight the interaction between control and learning and demonstrate the utility of active AM. In reality, epidemics are much more complex and there are likely to be multiple interacting uncertainties. For novel outbreaks, we may be unaware of the transmission characteristics in the early stages and therefore would not be able to fix the disease parameters as we have in this work. However, it may still be necessary to introduce a control policy rapidly despite the underlying uncertainty. In such circumstances, we are able to treat these parameters as we have vaccine efficacy, defining a prior distribution, possibly using historical data, and using active AM to implement an optimal multi-phase control policy that explicitly considers resolution of uncertainty as data are accrued during an outbreak. We would expect the potential of active AM to be even greater in such a scenario, when uncertainty is more prominent and therefore the correct course of action based on prior information alone is less clear. We attempt to address such scenarios in the coming chapters.

It is certainly true that following an active AM approach to management will never result in a worse outcome compared to following a passive or non-AM approach. However, in order to implement and benefit from such an approach in the real world, greater emphasis must be placed on ensuring the components of the AM framework are in place before making management decisions. That is, policy makers must have a clear idea of the objectives we wish to satisfy, the control options available and the data that is going to be collected throughout the outbreak, before making an initial control decision. This helps to avoid scenarios in which initial control hinders the resolution of uncertainty and our ability to make optimal control decisions in the future. Although, even if all components are clearly and quantitatively defined, the computational complexity of performing active AM can be a barrier to its implementation in real time [14], leading to the use of sub-optimal passive or non-AM approaches instead.

Whilst analyses of similar systems exist in the literature (e.g. [11, 58, 137]), this chapter has extended on such work in two main areas. First, we have applied the adaptive management methodology specifically to an infectious disease epidemiology context and explored in depth how passive and active AM methods can lead to contrasting recommendations at the start of an outbreak. Also, we have not relied upon metrics that assume the complete resolution of uncertainty, such as EVPI (Section 2.2; Equation 2.3), but rather defined a hypothetical, Bayesian method of uncertainty resolution that allows time-dependent, partial resolution of the uncertainty in vaccine efficacy. The methodology we have introduced in this paper

allows for the investigation of relatively unexplored areas in the epidemiological literature, for example the balance of resources between uncertainty resolution and control actions, an area that has received significant attention in the conservation and resource management literature [139–143] but less so for epidemiological interventions. It also allows us to clearly examine the effect that control actions can have on our ability to resolve uncertainty. In the context we have used, the resolution of uncertainty is directly linked to the control action available, as in similar applications in the literature (e.g. [59]), since we are not able to monitor vaccinations without administering them. This reinforces the idea of experimentation, which is a core part of the resilience-experimentalist side of AM [48]. However, in the next chapter, we show how active AM applies in a context where uncertainty is not directly linked to the control measures themselves, but rather the epidemiology of the disease. In such a context, we find that an active AM approach is still vital when making control decisions, over a passive or non-AM approach.

Chapter 4

Methods to anticipate uncertainty resolution

Abstract

We focus on the use of active AM in managing a theoretical epidemic with unknown transmission rate. Decisions centre around whether or not it is cost effective to implement a vaccination campaign. We compare three methods of anticipating the resolution of uncertainty in the future, an integral component of the active AM procedure: 1) a 'perfect information' method, which assumes that uncertainty in the transmission rate will be completely resolved, 2) an abstract method, which recognises that uncertainty will not be completely resolved, but the degree to which it is resolved is not linked to the state of the epidemic, and 3) a mechanistic method, which aims to explicitly model the mechanism behind uncertainty resolution, allowing partial resolution of uncertainty that depends on the state of the epidemic. We find that a mechanistic model of uncertainty resolution, used in conjunction with an active AM approach to management, is able to provide the most useful information to decision makers regarding the implementation and timing of both control and monitoring, significantly reducing the expected cost of the epidemic.

4.1 Introduction

In the previous chapter, we showed the importance of incorporating the uncertainty in the efficacy of control, and the future resolution of such uncertainty, into decisions made during the early stages of an outbreak. Using an active AM approach to

management, we are able to do so in a rigorous, structured way, improving outcomes and providing useful insights into the optimal delivery of control when compared to a non-AM or passive AM approach. This also exhibited the use of experimentation: implementing a control with uncertain effects, in order to gain a better understanding of these effects and ultimately improve management in the future.

However, in the event of a disease outbreak, not only the efficacy of control, but also the spread of the disease itself, is likely to be uncertain, especially during the early stages. Whilst it may not be a novel disease, the rate of transmission and recovery, among other parameters, is highly dependent upon the population and environment in which the outbreak is occurring. As such, it is necessary for management approaches to incorporate this uncertainty into decisions. In this chapter, address a scenario in which only the epidemiological parameters are unknown. We focus on a single source of uncertainty in the transmission rate, however also cover how these methods can be extended to multiple unknown disease parameters. In later chapters, we explore the effect of having uncertainty in both disease and control parameters.

Using a similar set-up as in the previous chapter, we explore our ability to make an optimal initial decision at the start of a disease outbreak, when the transmission rate is unknown. We focus on the use of an active AM approach, explicitly incorporating future uncertainty resolution into our initial decision. We emphasise again that such an approach can lead to different, preferable management recommendations compared to a non-AM or passive AM approach.

We extend our analysis of active AM significantly by investigating the method used to model and predict the resolution of uncertainty from real-time outbreak information. We define and analyse three methods: 1) a 'perfect information' method, assuming that uncertainty will be completely resolved by the time we make our final decision, 2) an abstract method, that allows partial resolution of uncertainty but does not depend directly on the state of the epidemic, and 3) a mechanistic method, which aims to model the monitoring process directly and link this to the uncertainty in parameters. We show that the first two methods, whilst able to provide some useful information, are highly limited in their utility. As such, we mainly use these as null models to highlight the importance of using the more complex, mechanistic method where possible.

We find that, using an active AM approach to management and aniticipating the effect of real-time information via a mechanistic model of uncertainty resolution can result in significantly improved management recommendations, reducing the expected cost of the outbreak when compared to non-AM and passive AM approaches.

Furthermore, by incorporating a mechanistic model of uncertainty resolution into the AM framework, we are able to optimise many aspects of both control and monitoring. These include: the timing of decision points and control implementation, the minimum requirements for monitoring effort, the optimal timing of samples used for monitoring and the optimal allocation of monitoring resources. In our example, using this information to optimise control and monitoring could reduce the expected cost of the outbreak by over 7%, compared to relying solely on prior information to make the initial decision. Over half of this reduction is gained from optimising the timing and allocation of monitoring resources during the early stages of the epidemic, something not possible without the combination of a mechanistic model of uncertainty resolution with the active AM framework.

Overall, we provide further motivation for the use of an active AM approach to epidemic management over passive or non-AM approaches, in the context of unknown epidemiological parameters. We demonstrate that anticipating the resolution of uncertainty, although not directly linked to the experimentation of control, has a significant effect on the recommended policy. Furthermore, using a mechanistic model for the resolution of uncertainty enables significant improvements to the timing and allocation of control and monitoring resources, greatly reducing the expected cost of the outbreak.

4.2 Adaptive management components

4.2.1 Model of system behaviour

We use the same basic epidemiological model as in the previous chapter to represent the spread of a directly transmitted disease. That is, a non-spatial, homogeneously mixing, deterministic SEIR model with constant transmission (β), incubation (σ) and recovery/removal rates (γ). Demography is ignored on the assumption that the dynamics of the epidemic are significantly faster that the natural birth-death process of the population. At the start of the outbreak, a single infected (I) individual is introduced into a population of 100,000 susceptible (S) individuals. We assume the outbreak is detected after a fixed amount of time (t_0), after which control can begin.

Vaccination of the population is the only form of control, implemented at a constant daily rate (ν_r), restricted by a finite vaccine pool (ν_{pool}) and effective with a fixed probability (ν_e). In contrast to the previous chapter, the vaccine efficacy is known. However, the vaccine is imperfectly targeted, being administered to both exposed (E) and susceptible (S) individuals proportional to their contribution to the

total population size. If an exposed individual is vaccinated, it will be ineffective and afford no immunity (represented by the V_E compartment). A vaccinated susceptible individual may gain complete, indefinite immunity, after a fixed delay, with probability ν_e (an 'effective' vaccination; moves to the V_1 compartment), or receive no immunity (an 'ineffective' vaccination; moves to the V_0 compartment). Each individual can only be vaccinated once. Further details of the system can be found in Figure 4.1.

The differential equations for the system are stated in Equation 4.1:

$$\begin{aligned}
\frac{dS(t)}{dt} &= -\beta\frac{S(t)I(t)}{N(t)} - \nu_r(t)\frac{S(t)}{S(t)+E(t)},\\
\frac{dE(t)}{dt} &= \beta\frac{S(t)I(t)}{N(t)} - \sigma E(t) - \nu_r(t)\frac{E(t)}{S(t)+E(t)},\\
\frac{dI(t)}{dt} &= \sigma(E(t)+V_E(t)) - \gamma I(t),\\
\frac{dR(t)}{dt} &= \gamma I(t) + \frac{V_1(t)}{\nu_d},\\
\frac{dV_0(t)}{dt} &= (1-\nu_e)\nu_r(t)\frac{S(t)}{S(t)+E(t)} - \beta\frac{V_0(t)I(t)}{N(t)},\\
\frac{dV_1(t)}{dt} &= \nu_e\nu_r(t)\frac{S(t)}{S(t)+E(t)} - \beta\frac{V_1(t)I(t)}{N(t)} - \frac{V_1(t)}{\nu_d},\\
\frac{dV_E(t)}{dt} &= \beta\frac{(V_0(t)+V_1(t))I(t)}{N(t)} + \nu_r(t)\frac{E(t)}{S(t)+E(t)} - \sigma V_E(t).
\end{aligned} \tag{4.1}$$

We define a vaccination campaign in the same way as in the previous chapter: $\mathcal{V}_{t_i,t_j}$ representing a campaign that starts on day t_i and ends on day t_j. If $t_i \leq t \leq t_j$, the campaign is ongoing and

$$\nu_r(t) = \begin{cases} \nu_r, & \text{if } S(t)+E(t) \geq \nu_r,\\ S(t)+E(t), & \text{if } 0 \leq S(t)+E(t) < \nu_r,\\ \nu_{pool} - \int_{t_i}^{t} \nu_r(s)\mathrm{d}s, & \text{if } \nu_{pool} - \int_{t_i}^{t} \nu_r(s)\mathrm{d}s < \nu_r,\\ 0, & \text{if } \int_{t_i}^{t} \nu_r(s)\mathrm{d}s > \nu_{pool}. \end{cases} \tag{4.2}$$

If $t < t_i$ or $t > t_j$, the campaign is not currently ongoing and $\nu_r(t) = 0$. If no vaccination occurs throughout the epidemic, we denote this by $\mathcal{V}_{0,0}$.

Finally, t_{end} represents the day on which the outbreak ends and hence the duration of the outbreak (relative to the time of detection). Given the continuous nature of the differential equations (Equation 4.1), we define this to be the point at which the

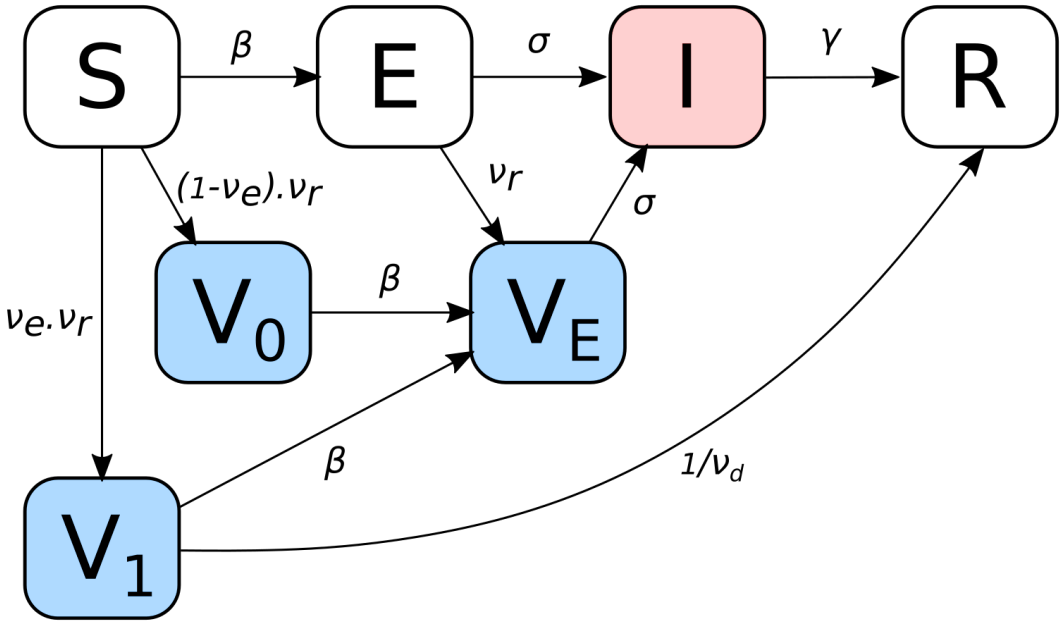


Figure 4.1: **Model of system behaviour.** We use a non-spatial, homogeneously mixing, deterministic Susceptible-Exposed-Infected-Removed (SEIR) model with vaccination as control. The transmission (β), incubation (σ) and recovery (γ) rates are constant throughout the epidemic. If a vaccination campaign is active, vaccination will occur at a constant daily rate ν_r (number of individuals per day), subject to the conditions outlined in Equation 4.2. The vaccine is imperfectly targeted towards both susceptible (S) and exposed (E) individuals. If a susceptible individual is vaccinated, it will be effective with probability ν_e and they will move into the V_1 compartment. At a rate of $1/\nu_d$ per day (ν_d representing the delay between vaccination and immunity), they will gain full, indefinite immunity, moving to the removed (R) compartment. Otherwise, if the vaccine is ineffective, they will move to the V_0 compartment where they remain completely susceptible to the disease. If an exposed individual is vaccinated, it will be completely ineffective and move to the V_E compartment, where it remains in the incubation stage before becoming infectious to others. Individuals that have been vaccinated but subsequently become infected (either due to an ineffective vaccine or not having yet developed immunity) also move to the V_E compartment. Blue shaded compartments identify vaccinated individuals and red shaded compartments infectious individuals.

number of Exposed (both vaccinated and unvaccinated) and Infectious individuals together falls below 1 ($E(t) + V_E(t) + I(t) < 1$). We use highly generic values to parametrise the model, however are similar to those of an influenza-like disease, for example. A description of the parameters and their default values throughout this chapter (unless otherwise specified) can be found in Table 4.1.

Table 4.1: **Summary of parameters and notation used.** Default values apply throughout unless otherwise stated. Values left blank depend on the vaccination campaign and are calculated as required during the optimisation process.

Notation	Description	Default value
β	Transmission rate of disease	Unknown
σ	Incubation rate of disease	0.5
γ	Recovery/removal rate from disease	0.2
ν_r	Daily vaccination rate (number of individuals)	1000
ν_e	Vaccine efficacy	100%
ν_{pool}	Total number of vaccines available	30000
ν_d	Delay between vaccination and immunity (days)	2
t_0	Detection and initial decision point (days after initial infection)	21
t^*	Final decision point (days after detection)	21
t_{end}	Day on which outbreak ends (duration of the outbreak)	-
V_{t_i,t_j}	Denotes a vaccination campaign that starts on day t_i and ends on day t_j. We require $t_0 \leq t_i \leq t_j \leq t_{end}$	-
$C(X \mid a_0, a_1)$	Cost of an outbreak X, conditioned on the initial and final decisions (defining the vaccination campaign) and the epidemiological parameters (excluded from notation for brevity).	-
ω_1	Weight assigned to the length of the outbreak (per day) in calculation of cost	0
ω_2	Weight assigned to each infection caused by the outbreak in calculation of cost	2.5
ω_3	Weight assigned to each vaccination administered in calculation of cost	1
ω_4	Weight associated with a fixed cost of implementing a vaccination campaign in calculation of cost	25000
k, θ	Parameters of the *Gamma* prior distribution around β, fixed by a specified mode and variance	Mode: 0.2 Var: 0.1
x, y	Parameters of the *Beta* prior distribution around γ, fixed by a specified mode and variance	Mode: 0.2 Var: 0.01
N	Total population size	100000

4.2.2 Objectives of management

We use the same flexible cost function introduced in the previous chapter to define the management objective, allowing the incorporation of the duration of the outbreak, number of infections caused by the outbreak, number of vaccinations administered and a fixed cost associated with implementing a vaccination campaign. Given initial and final decisions a_0 and a_1 (and epidemiological parameters; excluded from notation for brevity), the cost of an outbreak X is:

$$C(X \mid a_0, a_1) = \omega_1 \, t_{end} + \omega_2 \left(\int_0^{t_{end}} I(s) \mathrm{d}s \right) + \omega_3 \left(\int_{t_0}^{t_1} \nu_r(s) \mathrm{d}s \right) + \omega_4 \, \delta_V. \quad (4.3)$$

The goal of management is to minimise the expected cost of the outbreak, calculated by integrating the cost C over any uncertain parameters. Integrals are approximated using Monte Carlo integration.

The default weights used in the cost function (ω_i) throughout this chapter can be found in Table 4.1.

4.2.3 Optimisation approach

We continue with a two-step decision process: 1) an initial decision a_0 when the outbreak is detected on day t_0, and 2) a final decision a_1 on day t^*. At each decision point, we have a choice between vaccinating until the next decision point, or not (for the final decision, this equates to vaccinating until the vaccine pool is depleted, or not vaccinating until the end of the outbreak). These decisions are informed by prior information, available at the start of the outbreak, and real-time information that is collected between t_0 and t^*.

In this chapter, as in the previous chapter, we focus on the initial decision. We show how an active AM approach, aniticipating future learning, can be used to optimise different aspects of control and monitoring, minimising the expected cost of the outbreak. To do so, we will often refer to the expected cost of an initial decision, denoted $C(a_0)$, and the expected cost of an initial decision conditioned on the true parameters, $C(a_0 \mid \phi)$. The method of calculating both these values is given in Algorithm 1.

Note that Algorithm 1 describes the process of solving a MDP with two discrete time points ($t = \{0, t^*\}$) via SDP using backwards recursion (Equation 2.2). In this

case, the expected cost of an initial decision $C(a_0)$ is equivalent to the accumulated value of a decision $V_a(s_t, b(s_t))$, with $t = 0$. The expected cost of an initial decision conditioned on the true parameters, $C(a_0 \mid \phi)$, is equivalent to everything contained in the second line of Equation 2.2.

This is incorporated into the full active AM procedure as outlined in Algorithm 2. The four two-phase campaigns that can result from this decision making procedure are shown in Figure 4.2.

Algorithm 1 Calculate the expected cost of an initial decision

procedure ExpectedCost(a_0)
  repeat
    Draw unknown parameters (ϕ_0) from prior distributions
    Simulate epidemic (X) using Equation 4.1 and ϕ_0
    repeat
      Given epidemic X and/or ϕ_0, simulate an observation of real-time information (y_i)
      Given y_i, calculate posterior distribution $\pi(\phi \mid y_i)$
      for final decision $a_1 \in$ {do not vaccinate, vaccinate} **do**
        Calculate expected cost of final decision over posterior:
          $\mathbb{E}[C(X^* \mid a_0, a_1)] = \int_\phi C(X^* \mid \phi, a_0, a_1)\pi(\phi \mid y_i)d\phi$
      end for
      Choose final decision that minimises the expected cost:
        $A_i = argmin_{a_1}\{\mathbb{E}[C(X^* \mid a_0, a_1)]\}$
      Calculate the true cost of the final decision, conditioned on ϕ_0:
        $C(A_i) = C(X \mid a_0, A_i, \phi_0)$
    until a sufficient number of observations have been drawn
    Calculate the expected cost of this initial decision, conditioned on ϕ_0:
      $C(a_0 \mid \phi_0) = \int_i C(A_i) f(y_i \mid \phi_0)dy_i$
  until a sufficient number of draws of parameters have been made
  Calculate the expected cost of this initial decision:
    $C(a_0) = \int_{\phi_0} C(a_0 \mid \phi_0)\pi(\phi_0)d\phi_0$
end procedure

Algorithm 2 Active AM procedure

1: **for** initial decision $a_0 \in \{$do not vaccinate, vaccinate$\}$ **do**
2: Calculate expected cost of initial decision via Algorithm 1
3: **end for**
4: Choose initial decision with the lowest expected cost
5: Implement decision until t^*
6: On day t^*, use real-time information y to update probability distributions around unknown parameters
7: **for** final decision $a_1 \in \{$do not vaccinate, vaccinate$\}$ **do**
8: Calculate expected cost of final decision
9: $\mathbb{E}[C(X^* \mid a_0, a_1)] = \int_\phi C(X^* \mid \phi, a_0, a_1)\pi(\phi \mid y)d\phi$
10: **end for**
11: Choose the final decision that minimises the expected cost
12: Implement the final decision until the end of the epidemic, or the vaccine pool is depleted

4.2.4 Prior information and monitoring

For the majority of this chapter, we focus on a single source of uncertainty introduced by an unknown transmission rate β. We define our prior information regarding the transmission rate in a quantitative manner, using a $Gamma(k, \theta)$ distribution, where k and θ represent the shape and scale respectively. The probability density function for such a distribution is given by:

$$f(\beta; k, \theta) = \frac{\beta^{k-1} e^{-\frac{x}{\theta}}}{\theta^k \Gamma(k)}, \quad \beta, k, \theta > 0, \tag{4.4}$$

where $\Gamma(\cdot)$ is the Gamma function.

For clarity, we choose to define this distribution by its mode and variance:

$$\begin{aligned} \text{Mode} &= (k-1)\theta, \quad k \geq 1, \\ \text{Var} &= k\theta^2. \end{aligned} \tag{4.5}$$

Throughout this chapter, unless otherwise specified, we define the prior information around β using a *Gamma* distribution with mode = 0.2 and variance = 0.1 (see Figure 4.2). These values were chosen so that $\beta \leq 1$ (or equivalently $R_0 \leq 5$) approximately 95% of the time.

In later sections, we will also explore the effect of an unknown recovery/removal

rate (γ). We define our prior information regarding this rate using a $Beta(x, y)$ distribution with probability density function:

$$f(\gamma; x, y) = \frac{\Gamma(x+y)}{\Gamma(x)\Gamma(y)}\gamma^x(1-\gamma)^y, \quad x, y > 0,\ \gamma \in [0, 1]. \tag{4.6}$$

Again, we choose to define this distribution by its mode and variance:

$$\begin{aligned} \text{Mode} &= \frac{x-1}{x+y-2}, \quad x, y > 1, \\ \text{Var} &= \frac{xy}{(x+y)^2(x+y+1)}, \end{aligned} \tag{4.7}$$

setting them equal to 0.2 and 0.01 respectively.

Finally, we assume that real-time information is collected from the outbreak between the time of detection (and initial decision; t_0) and the final decision point (t^*). This information is combined with the prior information and used to reduce uncertainty in the epidemiological parameters. In this chapter, we compare three different methods of predicting how real-time information will affect the uncertainty in our parameters, detailed in the next section.

4.3 Modelling uncertainty resolution

A main focus of this chapter is the relationship between the real-time information being gathered during an outbreak and how it leads to uncertainty resolution, emphasising the need for a clearly defined, state-dependent model linking the two. We introduce three methods of modelling uncertainty resolution, with different levels of realism, and implement them within the AM framework. The two simpler methods act as null models, providing some useful information but largely serving as an example of why the third, more complex, model is preferred. We detail these methods here.

4.3.1 Perfect information

The simplest method of defining uncertainty resolution in the disease parameters is to assume that all uncertainty is resolved by the time we make our final decision at t^*. That is, we have 'perfect information'. This equates to having a posterior for β that is a single point, located at the true value, with every possible observation of real-time information leading to this result (Algorithm 1; steps 6 and 7). Whilst this

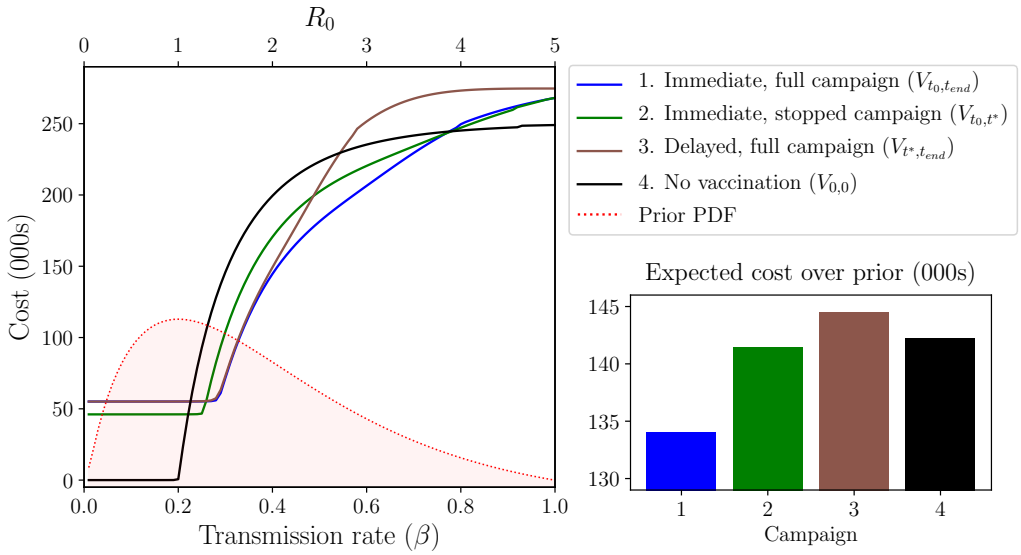


Figure 4.2: **Outbreak cost resulting from possible two-phase campaigns, assuming β is unknown but all other parameters are known and fixed.** Given our set-up with two decision points, an initial decision at $t_0 = 21$ and a final decision at $t^* = 42$, there are four possible two-phase campaigns that may be implemented by the end of the outbreak: 1) vaccination is started immediately (at t_0) and continued until the vaccine pool is depleted ($\mathcal{V}_{t_0,t_{end}}$; blue line), 2) vaccination is started immediately but stopped on day t^* ($\mathcal{V}_{t_0,t^*}$; green line), 3) vaccination is delayed until t^*, then implemented until the vaccine pool is depleted ($\mathcal{V}_{t^*,t_{end}}$; brown line), and 4) no vaccination throughout the outbreak ($\mathcal{V}_{0,0}$; black line). The main plot shows the predicted cost of the outbreak under each campaign calculated over a range of true transmission rates β using Equation 4.1. The smaller box plot shows the expected cost of each campaign, integrated over the prior distribution of β shown in the main plot in red. The values of other epidemiological parameters used and definition of the prior are given in Table 4.1.

method is unrealistic and has many limitations, it is useful for providing an upper bound for the benefit that can be gained from resolving uncertainty.

This method is similar to the EVPI measure (Section 2.2; Equation 2.3) used in VoI analysis. Whilst such a measure usually assumes perfect information at the current time, under this method of uncertainty resolution we assume perfect information in the future (on day t^*). We clarify this difference by defining a new measure, which we name the Expected Value of Future Perfect Information (EVFPI). Both measures in this context are detailed in Box 1.

Box 1: Quantifying the value of perfect information

In this box, we define and clarify the difference between the EVPI and EVFPI measures. We assume a scenario in which we have two decision points: an initial decision to vaccinate or not (a_0) and a final decision to vaccinate or not (a_1). The transmission parameter β is unknown, with prior distribution $\pi(\beta)$. The objective of management is to make decisions a_0 and a_1 that minimise the expected cost of the outbreak, where the cost of the outbreak, conditional on a given β, a_0 and a_1 is denoted $C(X \mid a_0, a_1, \beta)$.

Expected Value of Perfect Information (EVPI)

When calculating the EVPI, we assume that both decisions are made using perfect information:

$$\begin{aligned} EVPI = \int_\beta opt_{a_0,a_1} \left(C(X \mid a_0, a_1, \beta)\right) \pi(\beta) d\beta \\ - opt_{a_0,a_1} \left(\int_\beta C(X \mid a_0, a_1, \beta) \pi(\beta) d\beta \right) \end{aligned} \tag{4.8}$$

Expected Value of Future Perfect Information (EVFPI)

In contrast, we define the EVFPI to emphasise the fact that we will have perfect information for the final decision, but not for the initial decision:

$$\begin{aligned} EVFPI = opt_{a_0} \left(\int_\beta opt_{a_1} \left(C(X \mid a_0, a_1, \beta)\right) \pi(\beta) d\beta \right) \\ - opt_{a_0,a_1} \left(\int_\beta C(X \mid a_0, a_1, \beta) \pi(\beta) d\beta \right) \end{aligned} \tag{4.9}$$

For both measures (Equations 4.8 and 4.9), the calculation is the difference between two expected outcomes: the expected outcome given perfect information minus the expected outcome given only prior information. For EVPI (Equation 4.8), the first involves fixing β, then calculating the cost of the outbreak given all initial

and final decisions and choosing the optimal two-phase campaign. This is then integrated over all β according to the prior. Hence, given each value of β, we select the best two-phase campaign. This represents perfect information. The second expected outcome assumes prior information only: we calculate the cost of each campaign for all β, then integrate over the prior and choose the campaign which has the lowest expected cost across all β.

For EVFPI (Equation 4.9), the expected outcome under perfect information is different. For each value of β, we can only assume that the final decision will be made optimally, since, by the time we have perfect information, the initial decision will already have been made. Hence, for a given initial decision, we choose the optimal final decision at all values of β. We then choose the initial decision that gives the lowest expected cost after integrating over all final decisions according to the prior distribution of β. This will result in an outcome that is, at best, the same as in the calculation EVPI, but generally slightly worse (higher cost) given the delay in obtaining perfect information.

4.3.2 Abstract resolution

If we assume that uncertainty is not completely resolved before we make our final decision at t^*, and hence we do not have perfect information, we need to be able to define the uncertainty at t^* probabilistically. Such methods relate to the calculation of the EVSI (Section 2.2; Equation 2.5), in which we must predict what the posterior distribution of parameters will be, using the possible observations of data gathered in the future and the prior distribution of parameters.

The first method we use to do so is via an abstract definition of uncertainty resolution, summarised in Box 2. In this method, we assume that monitoring provides some number of abstract 'observations' of a process occurring at a constant rate β throughout the outbreak, providing a convenient definition of the posterior for β. This is incorporated into steps 6 and 7 of Algorithm 1. Whilst these observations are not grounded in reality, they allow us to partially resolve uncertainty, with the amount of resolution depending on the number of observations of the process. Since the process has a constant rate parameter β, this method of uncertainty resolution is completely detached from the state of the epidemic itself. As such, we use it as a null model to emphasise why it is important that our model of uncertainty resolution is closely linked to the epidemic and represents as closely as possible the real-time information that may be collected during an outbreak.

Box 2: Abstract uncertainty resolution procedure

In this box we outline the abstract method of estimating an unknown transmission rate (β) from real-time information collected throughout the outbreak.

Prior distribution

The prior distribution of β is based on a *Gamma* distribution with shape and scale (inverse rate) parameters k and θ (see Table 4.1 for values used):

$$\beta \sim Gamma(k, \theta) \quad (k\text{: shape, } \theta\text{: scale}) \tag{4.10}$$

Data

Between t_0 and t^*, we make n abstract observations of a process that occurs at a constant rate β:

$$\{x_i : 0 \leq i \leq n\}$$

Likelihood

The process we are observing occurs at constant rate β, hence each data point has likelihood:

$$x_i \mid \beta \sim Poisson(\beta) \tag{4.11}$$

Posterior

Using the conjugacy of the *Gamma* and *Poisson* distributions, we construct a posterior distribution of β from the observed data:

$$\beta \mid \{x_i\} \sim \text{Gamma}\left(k + \sum_{i=1}^{n} x_i, \frac{\theta}{n\theta + 1}\right) \tag{4.12}$$

4.3.3 Mechanistic resolution

The final definition of uncertainty resolution we introduce aims to directly link the information we might be getting from monitoring the outbreak and the uncertainty around parameters in a mechanistic way. We summarise this method in Box 3. Here, we explicitly define and model the collection of real-time information via a number of cross-sectional samples of the population, identifying individuals in the samples who are currently infectious. We assume that all infectious individuals are symptomatic and will be correctly identified if contained within a sample, whereas exposed individuals are asymptomatic and will be missed. There is also no misclassification of healthy individuals as infected. The number of infectious individuals found in each sample is used on day t^* to estimate the posterior distribution of disease

parameters via a Bayesian fitting procedure. This is incorporated into steps 6 and 7 of Algorithm 1. Since the occurrence of infectious individuals within a sample depends on the total number of infections in the population, this method of uncertainty resolution directly depends on the state of the epidemic.

When implementing this definition within the AM framework, it is necessary to draw likely observations $\{d_i : 0 \leq i \leq C\}$ given a value of β (Algorithm 1; step 6). Given our use of a continuous, deterministic SEIR model, it is possible that we may observe infections in our samples, even if the number of infected individuals in the population is below 1. To combat this, we assume that if $R_0 < 1$, we will not observe any infections in the population (i.e. if $R_0 < 1$, $d_i = 0$ for all i).

Box 3: Mechanistic uncertainty resolution procedure

In this box we outline the mechanistic method of estimating an unknown transmission rate (β) from real-time information collected throughout the outbreak.

Prior distribution

The prior distribution of β is based on a *Gamma* distribution with shape and scale (inverse rate) parameters k and θ (see Table 4.1 for values used):

$$\beta \sim Gamma(k, \theta) \quad (k\text{: shape, } \theta\text{: scale}) \tag{4.13}$$

Data

The real-time information is made up of C data points $\{d_i : 0 \leq i \leq C\}$, representing the number of infectious individuals detected from C cross-sectional samples of the population taken at times $\{t_i : t_0 \leq t_i \leq t^*\}$ during the outbreak. The size of each sample is denoted M_i.

Likelihood

The number of infectious individuals observed in each sample depends on the prevalence of the disease in the population at that time and the size of the sample:

$$d_i \mid \beta \sim Binom\left(\frac{I(t_i)}{N(t_i)}, M_i\right), \tag{4.14}$$

where I, N are calculated via Eq 4.1 conditional on β.

Posterior

We implement a Hamiltonian Monte Carlo (HMC) fitting procedure using the Stan programming language (Section 2.3.2), interfacing with Python via PyStan, to obtain posterior distributions of β and cost under different controls.

Approximation

A major issue with this method is the computational complexity required: we must draw many observations d_i, for many values of β, and perform a fitting process on each set of observations to obtain a posterior and predict the optimal final decision. Whilst this is plausible for a single set of parameters, if we are trying to optimise control and monitoring, as we do in subsequent sections, it quickly becomes intractable. However, we have found that we can accurately approximate this process under some acceptable conditions.

The approximation arises from the observation that, for smaller sample sizes ($\lessapprox 8000$), and $0 < \beta < 0.55$ ($0 < R_0 < 2.75$), we will only make a final decision not to vaccinate if we do not detect any infectious individuals across all samples. Hence, we approximate the expected cost of an initial decision by assuming that we will make a final decision not to vaccinate if no infections are detected in all the samples, otherwise we will make a final decision to vaccinate. The approximation is summarised in Algorithm 3, replacing lines 7 - 18 in Algorithm 1 with a single equation (line 6).

Algorithm 3 Approximate the expected cost of an initial decision (a_0)

1: **procedure** ExpectedCost(a_0)
2: **repeat**
3: Draw unknown parameters (ϕ_0) from prior distributions
4: Simulate epidemic (X) using Equation 4.1 and ϕ_0
5: Calculate the expected cost of this initial decision, conditioned on the parameter values drawn:
6: $C(a_0 \mid \phi_0) = C(X \mid \mathcal{V}_{0,0}, \phi_0)P(y_i = \bar{0}) + C(X \mid \mathcal{V}_{t^*,t_{end}}, \phi_0)P(y_i \neq \bar{0})$
7: **until** a sufficient number of draws of parameters have been made
8: Calculate the expected cost of this initial decision:
9: $C(a_0) = \int_{\phi_0} C(a_0 \mid \phi_0)\pi(\phi_0)d\phi_0$
10: **end procedure**

Finally, for an initial decision not to vaccinate, if $\beta > 0.55$ the optimal final decision is to continue without vaccination, since the epidemic will have progressed far enough that implementing a campaign at this stage is no longer worthwhile. Given the sharp switch we see in the results using the full procedure (see Figure 4.4), in the approximation we will assume that, for $\beta > 0.55$, we will behave as if we had perfect information.

This approximation is accurate under the following three conditions:

Maximum sample size Each sample must contain a maximum of 8000 individuals, else the assumption that only $d_i = 0$ for all i will lead to a final decision not to vaccinate is no longer true.

Minimum sample size When calculating the expected cost of an initial decision not to vaccinate, it is necessary that each sample contains at least 500 individuals, else even obtaining $d_i = 0$ for all i is not enough to recommend no vaccination as the final decision. For samples below this size (until the sample size drops below approximately 10 per sample), the posterior will always lead to a final decision to vaccinate, since a delayed campaign results in a lower expected cost than no vaccination. At extremely low sample sizes (less than approximately 10), the posterior is very similar to the prior, hence this will lead to a final decision not to vaccinate. This condition also holds for an initial decision to vaccinate, however the minimum sample size is higher at approximately 1500 individuals.

Minimum number of samples It is necessary to have at least 4 samples to ensure a realistic fit from the fitting procedure. Fewer samples than this can lead to convergence on a very high value of β, representing an epidemic that peaks and dies out again within the sampling period.

To test this approximation, we use it to calculate the expected cost of an initial decision not to vaccinate, across a range of sample sizes, and compare this to what we obtain using the full procedure for three specific sample sizes (2000, 4000 and 6000 individuals per sample; Figure 4.3). We find an almost exact match between the two methods.

4.4 Comparison of uncertainty resolution models

We compare how our view of the initial decisions and their outcomes change under each model of uncertainty resolution (Figure 4.4). In the top row, we show the expected cost of both initial decisions across a range of true values of β (Algorithm 1; step 18, discretised into fixed intervals of β), for each of our methods of uncertainty resolution. The bottom row shows the expected cost of each campaign under the prior distribution (bars) and the expected cost of both initial decisions (dashed lines), for each method of uncertainty resolution.

Under all methods, we observe a similar result as in the previous chapter. Following a non-AM or passive AM approach to management, we do not anticipate the resolution

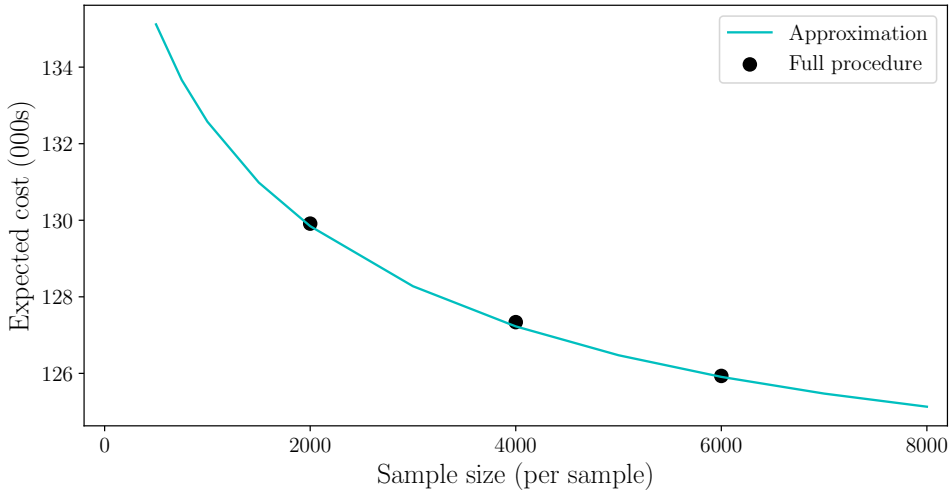


Figure 4.3: **Comparison of full mechanistic method and approximation.** We compare the expected cost of an initial decision not to vaccinate using the original definition of the mechanistic method of uncertainty resolution (Box 3) and our approximation (Algorithm 3), for three specific sample sizes. We assume that samples are taken on at equally spaced intervals between the time of detection t_0 and t^*: $\{t_i\} = \{21, 28, 35, 42\}$. The transmission rate β is unknown with a *Gamma* prior, all other parameters are given in Table 4.1.

of uncertainty in β, leading to an initial recommendation to vaccinate, since an immediate, full campaign is optimal under the prior. However, following an active AM approach, we would recommend not vaccinating until t^* before deciding whether or not vaccinate. This allows us to avoid the cost of implementing a vaccination campaign if β is likely to be low and therefore $R_0 < 1$, since the outbreak will quickly die out by itself, leading to a lower expected cost. Or if β is very high ($\beta > 0.55$), for which a vaccination campaign no longer has a large enough impact to be considered cost effective. Thus, anticipating the future resolution of uncertainty can change our initial decision even if uncertainty resolution does not rely on the implementation of control.

Under the assumption of gaining perfect information by t^* (Figure 4.4 (A)), we observe sharp changes in the expected cost across varying true values of β, where the optimal campaign changes. For example, if we make an initial decision not to vaccinate, our final decision will be between not vaccinating throughout, or implementing a delayed, full vaccination campaign. When making this final decision, we know exactly what the true value of β is (because we have perfect information): if $\beta \leq 0.2$, then we will choose not to vaccinate, if $0.2 < \beta \leq 0.55$, we will choose to start vaccinating, and if $\beta > 0.55$, we will again choose not to vaccinate. There is no uncertainty in our decision around these points, hence we will never make the wrong

final decision (i.e. start vaccinating when we should not, or vice versa). We can make similar assumptions for an initial decision to vaccinate. Overall, we find that waiting until t^*, rather than vaccinating immediately, leads to a 6% lower expected cost. We calculate EVFPI = 11534 (Equation 4.9; same units as the objective function, e.g. currency), here representing the difference between the expected cost of the decision made with only prior information (an immediate, full campaign) and the expected cost of the decision made assuming perfect information at t^* (no immediate vaccination, with vaccination starting at t^* only if $0.2 < \beta \leq 0.55$). This is equivalent to an 8% decrease in the expected cost.

Using the abstract definition of uncertainty resolution (Figure 4.4 (B)), assuming 50 observations of a process occurring at a constant rate β, we no longer have sharp transitions between campaigns, due to the remaining uncertainty in β when we make our final decision. For example, under an initial decision not to vaccinate, if $\beta \approx 0.2$ (and hence $R_0 \approx 1$), there remains significant uncertainty as to whether starting a delayed campaign or continuing without vaccination is the optimal choice, resulting in the possibility of making the wrong final decision. Under the assumption of perfect information, this uncertainty does not exist. Hence, the expected cost of both initial decisions is increased, with an initial decision not to vaccinate being affected the most, since the disparity between expected cost at low and high values of β is much greater under this initial decision (which, conversely, also allows it to provide larger benefits). However, the initial recommendation is unchanged: not vaccinating immediately and making a final decision based on updated information provides the lowest expected cost. We use the EVSI measure (Equation 2.5) to calculate the value of partially resolving uncertainty. Under the abstract method, we obtain EVSI = 6255, just over half of the benefit of resolving uncertainty completely.

Finally, under the mechanistic definition of uncertainty resolution with 4 samples of 4000 individuals each (Figure 4.4 (C)), we see a similar result, with increased expected costs compared to when we assume perfect information, but an initial decision not to vaccinate remaining optimal. We also observe a very similar expected cost for both initial decisions compared to the abstract definition, suggesting that 50 abstract 'observations' may in some way equate to the same amount of uncertainty resolution as the four samples of 4000 individuals taken in the mechanistic method. We explore this in further detail in later sections. In this case we calculated EVSI = 6392, slightly greater than under the abstract method. We again see increased uncertainty around points where the optimal campaign changes, compared to when we assume perfect information, however, the magnitude and effect of this uncertainty is significantly different from what we observe under the abstract method. Under

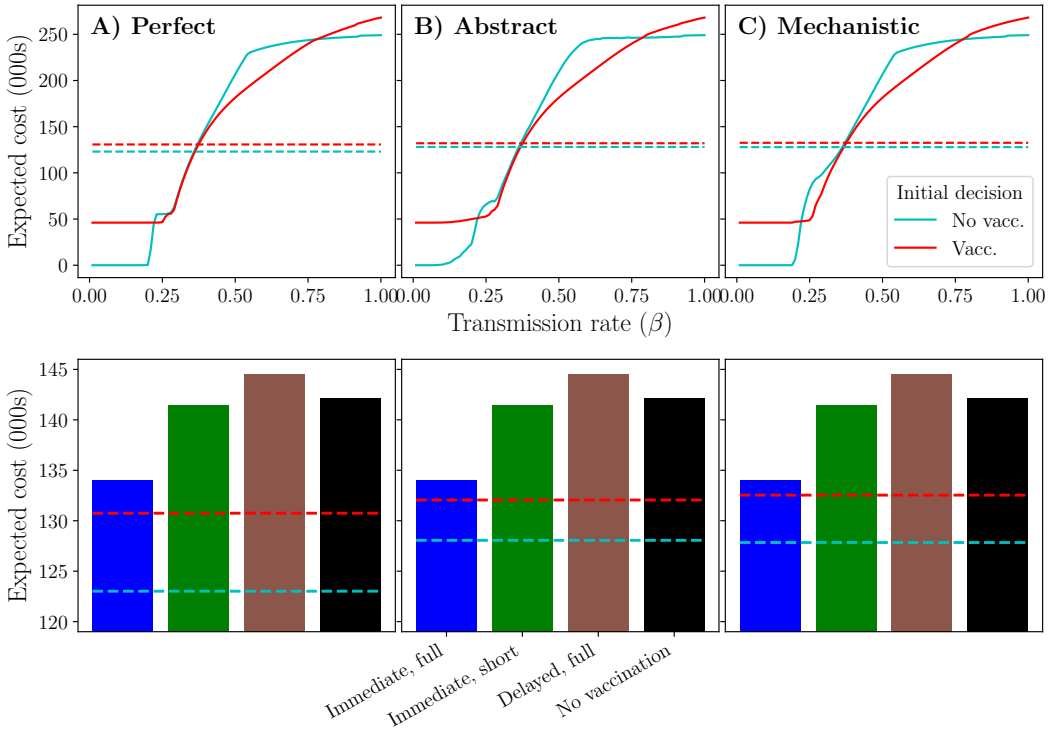


Figure 4.4: **Expected cost of initial decisions using different methods of modelling uncertainty resolution.** Top row: solid blue and red lines show the expected cost of initial decisions (not to vaccinate and to vaccinate respectively) for a range of true values of the transmission rate β (Algorithm 1; step 18). Dotted lines give the expected cost of the initial decision integrated over the prior distribution of β (Algorithm 1; step 21). The method of incorporating uncertainty resolution into predictions is split across columns: A) assuming perfect information at t^* (Box 1), B) using the abstract method of uncertainty resolution with $n = 50$ (Box 2), and C) using the mechanistic method of uncertainty resolution with four samples of 4000 individuals taken on days $\{21, 28, 35, 42\}$ (Box 3). Bottom row: expected cost of each two-phase campaign integrated over the prior distribution of β (bars), alongside the expected cost of initial decisions (dotted lines). The possible two-phase campaigns are 1) an immediate, full campaign ($\mathcal{V}_{t_0,t_{end}}$; blue bar), 2) an immediate campaign that is stopped on say t^* ($\mathcal{V}_{t_0,t^*}$; green bar), 3) a delayed, full campaign ($\mathcal{V}_{t^*,t_{end}}$; brown bar), or 4) no vaccination throughout the outbreak ($\mathcal{V}_{0,0}$; black bar). Values of parameters used are given in Table 4.1.

the abstract method, the uncertainty changes smoothly around points where the optimal campaign changes, increasing as we approach such a point and decreasing to zero away from it. Under the mechanistic definition however, we see that the uncertainty depends heavily on the value of β: leading up to $\beta = 0.2$, a point where the optimal campaign changes, there is no uncertainty in our choice, since we know we will not observe any cases and therefore will always choose not to vaccinate. However, this quickly changes as we increase past this point, since there is now a significant possibility of not observing any cases simply because our sample missed them, hence resulting in a suboptimal decision not to vaccinate. As β increases further, the probability of this occurring falls, since there will be more infections in the population. For high values of β, we also see a sudden switch back to not vaccinating, almost as if we had perfect information, whereas in an abstract setting this change is gradual.

Hence, although the expected cost of each initial decision does not appear to change significantly between the abstract and mechanistic methods of modelling uncertainty resolution, there are substantial differences in the behaviour of the expected cost conditional on the true value of β. This is due to the fact that, whilst the abstract method only depends on a constant β through the *Poisson* likelihood (Eq 4.11), the mechanistic method takes into account the fact that the amount of uncertainty resolved may depend on the state of the epidemic itself.

For the abstract method, we see increasing variance in the posterior at higher values of β (Figure 4.5; left): since the variance of a $Gamma(k, \theta)$ distribution is equal to $k\theta^2$, and the posterior of β given observations $\{x_i\}$ is Gamma $\left(k + \sum_{i=1}^{n} x_i, \frac{\theta}{n\theta+1}\right)$ (Equation 4.12), we expect the variance to increase at higher values of β via an inflated sum $\sum_{i=1}^{n} x_i$.

However, for the mechanistic method we see the opposite (Figure 4.5; right): if $\beta < 0.2$, the outbreak dies out immediately and we will not observe any infections in the samples, resulting in the same posterior for all such values of true β. As β increases above 0.2, the outbreak will no longer die out quickly and we are likely to observe some infections. The higher the true value of β, the more infections we expect to observe and hence we obtain thinner posteriors. This highlights the importance of having a clear link between the resolution of uncertainty and the state of the epidemic itself.

Overall, we see that the method of incorporating uncertainty resolution into our predictions of campaign performance can have a significant effect on the expected cost of the outbreak and therefore our initial decision. As such, we should aim to

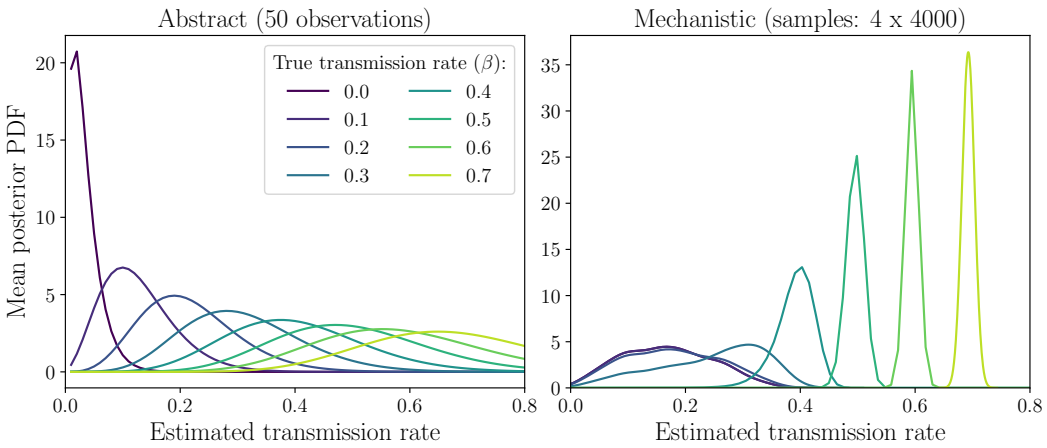


Figure 4.5: **Comparison of mean estimated posteriors under abstract and mechanistic methods of uncertainty resolution.** We simulate posterior distributions of β using the abstract (Box 2; Eq 4.12) and mechanistic (Box 3) methods of uncertainty resolution, for a large number of possible data points drawn from likelihoods conditional on the true value of β. Here we show the mean posterior from simulations for a number of values of true β. Values of parameters used are given in Table 4.1.

model the relationship between real-time information and system uncertainty as accurately as possible. Throughout the rest of this chapter, we show how active AM, in conjunction with these methods, can be used to further optimise the delivery of control and gathering of real-time information.

4.5 Optimising monitoring and control

In the following sections we show how active AM can be used to optimise monitoring and control when the disease parameters are unknown. We focus on the situation where only the transmission rate β is unknown and the incubation and recovery rates (σ and γ) are known and fixed, to clarify explanation. However, the final section addresses the extension of these methods to more unknowns. We use all three methods of uncertainty resolution where possible, using the perfect information and abstract methods as null models to highlight the greater utility and accuracy of the mechanistic method. We focus mainly on optimising the expected cost of an initial decision not to vaccinate, since this is already the optimal initial decision (Figure 4.4) and responds the most to real-time information.

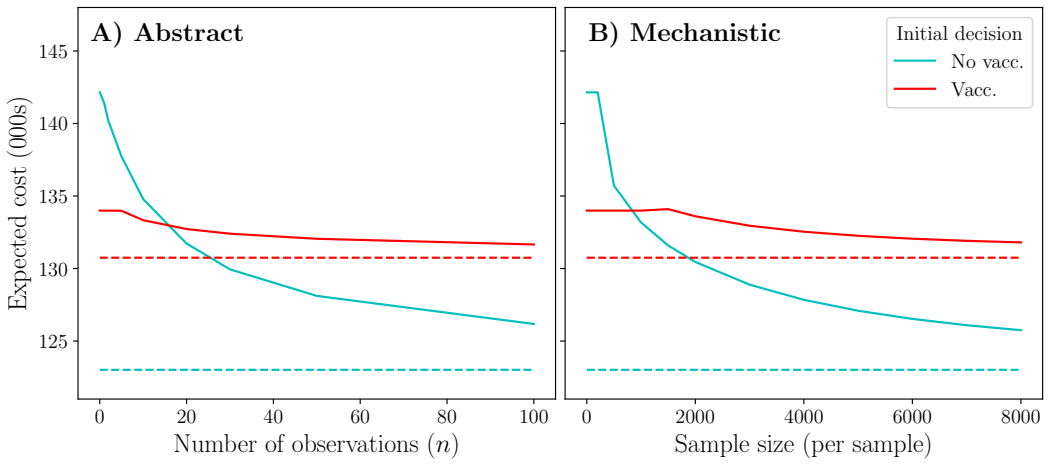


Figure 4.6: **Effect of the amount of monitoring performed on the expected cost of initial decisions.** A) for the abstract method, we vary the number of observations n of a process that occurs at a constant rate β (Box 2). A larger number of observations results in a thinner posterior for β. B) for the mechanistic method, we vary the sample size of four cross-sectional samples of the population, taken on days $\{21, 28, 35, 42\}$. Larger samples will result in thinner posteriors of β. Dashed lines show the expected cost obtained using the perfect information assumption. Values of parameters used are given in Table 4.1.

4.5.1 Amount of monitoring

We begin by analysing the effect of changing the amount of monitoring that is performed, which directly relates to the amount of uncertainty that is resolved by the time we make the final decision at t^* (Figure 4.6). A limitation of assuming perfect information at time t^* is it does not allow us to consider this factor. However, using the abstract and mechanistic methods of uncertainty resolution, we are able to analyse the effect of resolving more or less uncertainty on our ability to minimise the expected outbreak cost.

Under the abstract method, this is achieved by changing the number of observations n (Box 2), and under the mechanistic definition by changing the size of each sample M_i (Box 3). Note, here we assume a constant sample size across samples ($M_i = M_j, \forall i, j$). The expected cost under perfect information is given as reference (Figure 4.6; dashed lines). We see that, as the amount of uncertainty resolved increases under both definitions, the expected cost of both initial decisions falls, although significantly more so for an initial decision not to vaccinate than to vaccinate. This is due to the greater disparity in expected cost between low and high values of β for the former. Both methods highlight the benefit of waiting until t^* to vaccinate (or not), conditional on enough monitoring information being gathered

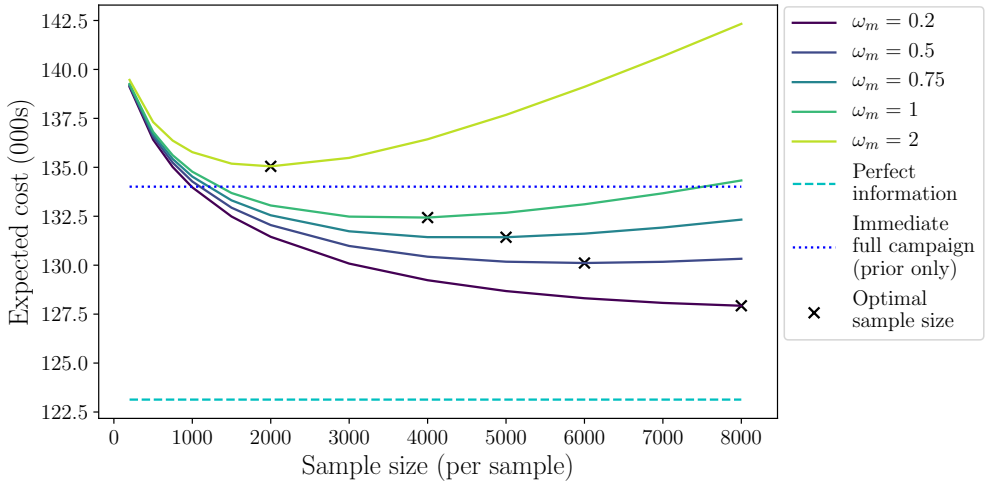


Figure 4.7: **Effect of an explicit monitoring cost on the expected cost of an initial decision not to vaccinate.** Using the mechanistic method of uncertainty resolution, we assign an explicit cost to each individual sampled (ω_m), relative to the cost of a single vaccination. We vary the value of ω_m and calculate the expected cost of an initial decision not to vaccinate over a range of sample sizes. For each value of ω_m, we identify the sample size which minimises the expected cost with a black 'x'. The expected cost assuming perfect information and prior information only are shown by dashed and dotted lines respectively. The values of parameters used can be found in Table 4.1.

(at least approximately 15 observations, $n = 15$, or 1000 individuals per sample, $M_i = 1000$).

Both methods display a very similar relationship between the amount of uncertainty resolved and the expected cost of the outbreak, with the rate of decrease in expected cost falling as more uncertainty is resolved. Comparing the expected cost between the two, it appears that our abstract idea of an observation resolves as much uncertainty as 4 samples of 80 individuals. If we associated a cost with each observation or individual in a sample, we could identify a clear optimal to minimise the overall expected cost, with a higher monitoring cost leading to a lower optimal sample size or number of observations (Figure 4.7). If the monitoring cost is very high (e.g. $\omega_m = 0.2$), the benefit of waiting until t^* to decide whether or not to vaccinate may be outweighed by the cost of monitoring, causing immediate, full vaccination, without monitoring, to become the optimal initial decision.

4.5.2 Sample frequency

A limitation of the abstract method of uncertainty resolution is that the only factor affecting the resolution of uncertainty is the total number of observations n achieved by t^*. However, the mechanistic method allows us to go further and analyse the effect of sample timing, frequency and the distribution of sampling resources. Thus far, for the mechanistic method, we have assumed that we have four sample points ($C = 4$), taken at equally spaced intervals between the time of detection t_0 and t^* ($t_i = \{21, 28, 35, 42\}$), with the same number of individuals within each sample.

We vary the frequency of samples, whilst keeping the overall number of individuals contained across all samples the same (Figure 4.8). We still assume that samples are taken at equally spaced intervals between the time of detection and t^* and with a constant sample size across samples. Overall, this does not greatly affect the expected cost of the outbreak. However, it is clear that fewer samples, with a larger number of individuals in each sample, is preferred, due to there being a slightly lower probability of not observing any cases in the population across all samples for $1 < R_0 < 2$ ($0.2 < \beta < 0.4$). Note, however, that care needs to be taken at a low number of samples, since this can cause the fitting procedure to not converge or converge on a very high value for β. As a result, it is not feasible to use only 2 or 3 samples for such a fitting procedure, as it does not produce consistent results. Hence, throughout our analyses we use at least 4 samples. In reality, it is likely we will be restricted as to how many individuals can be tested for the disease at one time, hence, this would also restrict our ability to perform a low number of very large samples. Similarly, for a high number of samples, we must ensure that each sample is large enough that the minimum sample size condition is met (Section 4.3.3).

4.5.3 Distribution of sampling resources

We find that removing the assumption that all four samples are of equal size, whilst keeping a constant overall sample size $\left(\sum_{i=1}^{C} M_i = 12000\right)$, can have a significant effect on the expected cost of our initial decision (Figure 4.9). We do so by defining a distribution of resources applied across the four sample points. We use a $Beta(\alpha, \xi)$ distribution to split the total sample size between points, allocating $x_1 = F(0.25) \cdot \sum_{i=1}^{C} M_i$ to the first sample, $x_2 = (F(0.5) - F(0.25)) \cdot \sum_{i=1}^{C} M_i$ to the second sample etc, where F is the CDF of the *Beta* distribution. We vary both the location of the mode $\left(\frac{\alpha-1}{\alpha+\xi-2}\right)$ and the concentration $\alpha + \xi$, providing a measure of how clustered around the mode the distribution is. Note that, for $\alpha + \xi = 1$, there are two modes of the distribution at 0 and 1 (however one may be significantly more prominent

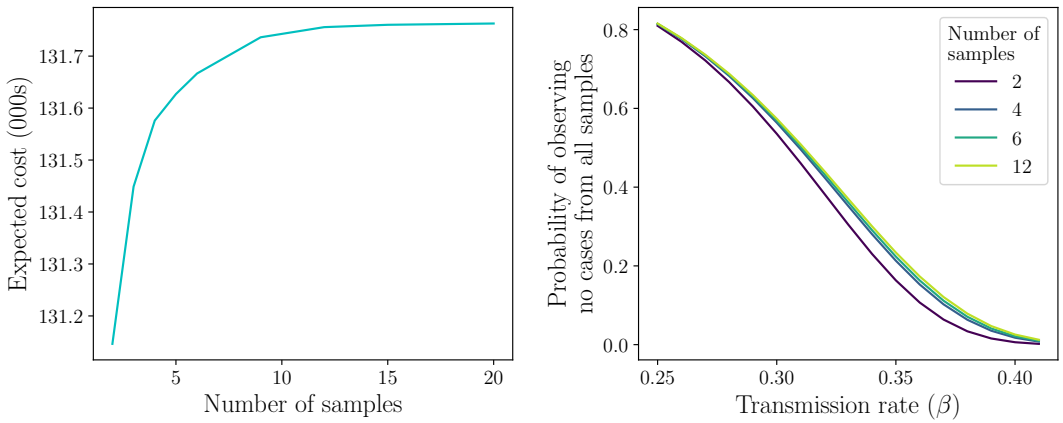


Figure 4.8: **Effect of the number of samples on the expected cost of an initial decision not to vaccinate.** Using the mechanistic method of uncertainty resolution, we vary the number of samples C whilst keeping the total sample size constant ($\sum_{i=1}^{C} M_i = 10000$). The left-hand plot shows the expected cost of an initial decision not to vaccinate for different numbers of samples. The right-hand plot shows the probability of observing no cases across all the samples, across a small range of β for which cases will exist in the population ($R_0 > 1$) but in low numbers. The values of parameters used can be found in Table 4.1.

than the other), and for $\alpha + \xi = 2$, the sample size is constant across all samples, as we have assumed so far. We also enforce a minimum sample size of 500 individuals per sample, to allow us to use our approximation of the expected cost (Algorithm 3; Section 4.3.3). We find that allocating as many resources as possible to the final sample is optimal for minimising the expected cost, reducing it by a further 1% compared to using a constant sample size. This is because, for this epidemic, we expect the number of infections in the population to continue increasing past day 42, thus the number of infections will be greater on the last sample day ($t = 42$) compared to earlier sample days. Therefore, taking a large sample on the last day minimises the probability of not observing any infections across all our samples if infections are in fact present in the population. Conversely, allocating most resources to the first sample day ($t = 21$) has the opposite effect for the same reason.

4.5.4 Timing of sampling and control

So far, we have assumed that the time of the final decision, t^*, is fixed. We now remove this assumption and analyse the benefits of optimising this parameter also. If we ignore the effect of uncertainty resolution when making our initial decision, as we would in a passive AM context, we would always seek to make our final decision as early as possible, since implementing a vaccination campaign earlier makes it

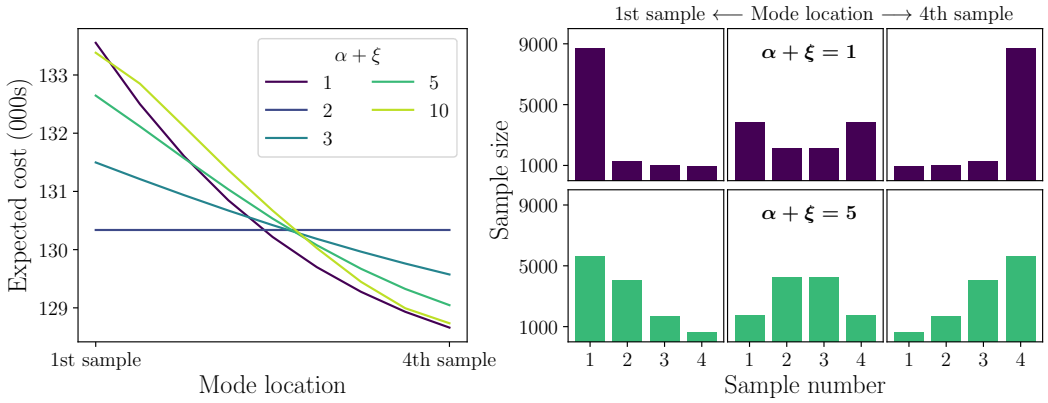


Figure 4.9: **Effect of sample size distribution on the expected cost of an initial decision not to vaccinate.** We vary the distribution of sampling resources across four samples using a $Beta(\alpha, \xi)$ distribution to split the total sample size $\left(\sum_{i=1}^{C} M_i = 12000\right)$ unevenly across the samples. We allocate $x_1 = F(0.25) \cdot \sum_{i=1}^{C} M_i$ to the first sample, $x_2 = (F(0.5) - F(0.25)) \cdot \sum_{i=1}^{C} M_i$ to the second sample etc, where F is the CDF of the *Beta* distribution. We vary both the location of the mode $\left(\frac{\alpha-1}{\alpha+\xi-2}\right)$ and the sum $\alpha + \xi$, providing a measure of how clustered around the mode the distribution is. The left-hand plot shows the expected cost of an initial decision not to vaccinate for a range of distributions. The right-hand plots show the allocation of sampling resources across the four samples for a selection of the distributions tested. The values of parameters used are given in Table 4.1.

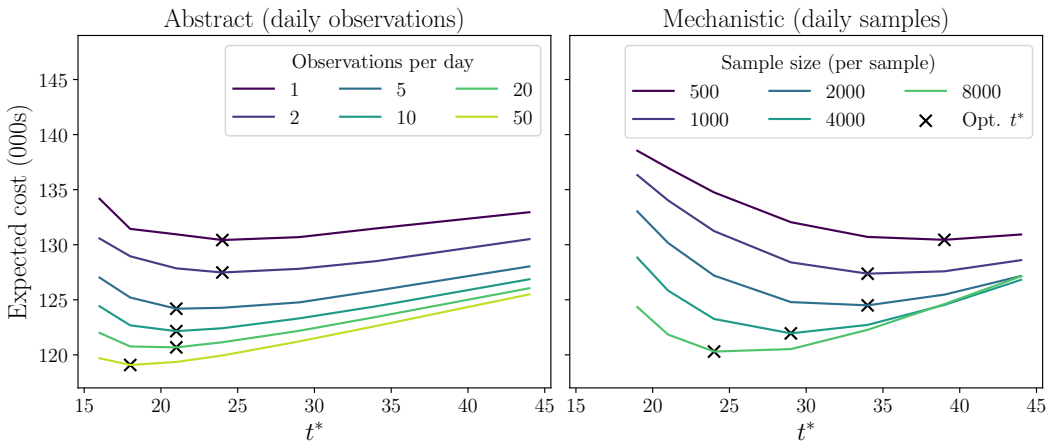


Figure 4.10: **Optimising the time of the final decision, t^*, under different rates of uncertainty resolution.** We calculate the expected cost of an initial decision not to vaccinate for a range of t^* and rates of uncertainty resolution. Left: using the abstract method of uncertainty resolution with 1 - 50 observations per day. Right: using the mechanistic method of uncertainty resolution with daily samples of sizes 500 - 4000. The value of t^* that gives the lowest expected cost is shown with a black 'x'. The values of parameters used can be found in Table 4.1.

more effective. However, this reduces the time we have to resolve uncertainty. When viewed in an active AM context, we see that there is a balance between fast control and waiting to learn more about the transmission parameters.

For both the abstract and mechanistic methods of uncertainty resolution, we optimise the value of t^* for different rates of uncertainty resolution (Figure 4.10). In both cases, we see that waiting at least a few days to gain information on the transmission rate leads to an improved expected cost. The slower the rate of resolution, the longer this optimal delay is. However, we also note that, under the abstract method we tend to recommend a shorter optimal delay than under the mechanistic method. This is again the result of the abstract method not taking into account the state of the epidemic, hence it assumes that uncertainty is resolved consistently over time. This is not the case, since monitoring resources may lead to more uncertainty resolution later on in the outbreak, when it would be easier to detect cases if there are any, compared to the very start of the outbreak. Using the mechanistic method of uncertainty resolution, we are able to recognise this and optimise monitoring accordingly, recommending longer delays between initial and final decisions to allow for more effective monitoring (Figure 4.10).

We take the analysis of sample timing further using the mechanistic method: instead of assuming 4 samples equally spaced between $t = 21$ and 42, we vary the

sample times ($\{t_i : 0 \leq i \leq 4\}$) by taking all possible combinations of 4 sample points spaced 2 days apart between $t = 21$ and 42 (Figure 4.11). We find the timing of samples can have a significant effect on the expected cost of an initial decision not to vaccinate (Figure 4.12). We analysed the effect of sample timing under two different assumptions: first, that the final decision is always made on day 42, regardless of the sample times ($t^* = 42$; top row), and second, that the final decision is made immediately after all four samples have been collected ($t^* = t_4$; bottom row). We see that the behaviour of the expected cost for different sample times changes significantly under these assumptions.

If t^* is fixed at 42, we see that it is best to have all the samples as late as possible, to maximise the probability of finding cases if there are any (since the number of infections in the population, if there are any, will still be increasing at $t = 42$). The sample size has little effect on this behaviour (Figure 4.12; columns), although a higher sample size reduces the expected cost under all timings, as we would expect from Figure 4.6. A higher sample size also appears to reduce the effect that sample timing has on the expected cost, shown by a lower variation, which is intuitive since we are less likely to miss any infections and thus depend less on the prevalence in the population. By taking samples as late as possible, i.e. on days $\{35, 37, 39, 41\}$, as opposed to equally spaced between days 21 and 42 (inclusive), we reduce the expected cost of an initial decision to wait by 1% for a sample size of 2000 and 0.8% for a sample size of 5000.

If t^* is set to the final sample point, that is, we make the final decision as soon as the four samples have been taken, we see very different, more complex dynamics. This arises from the interplay between having an earlier final decision, which improves the efficacy of vaccination campaigns, and the increased uncertainty resolution from having later samples, discussed previously. As a result, in some cases, neither having all the samples as late as possible nor as early as possible is optimal, but rather we should balance the two. This is highly dependent on the sample size. For large samples, having later samples has less of an effect on our ability to resolve uncertainty, since it can be well resolved by large samples even at early stages of the outbreak. Hence, the improved efficacy of an early final decision largely outweighs the benefit of later samples. Conversely, for smaller samples, we observe the opposite and the optimal timing of samples is pushed later. However, it is still the case that all the samples should be taken as close together as possible. We also see that larger samples result in higher variance of expected cost between different sample times, the opposite to what we observe if the final decision point is fixed, since delaying control when uncertainty is already sufficiently resolved has relatively more impact.

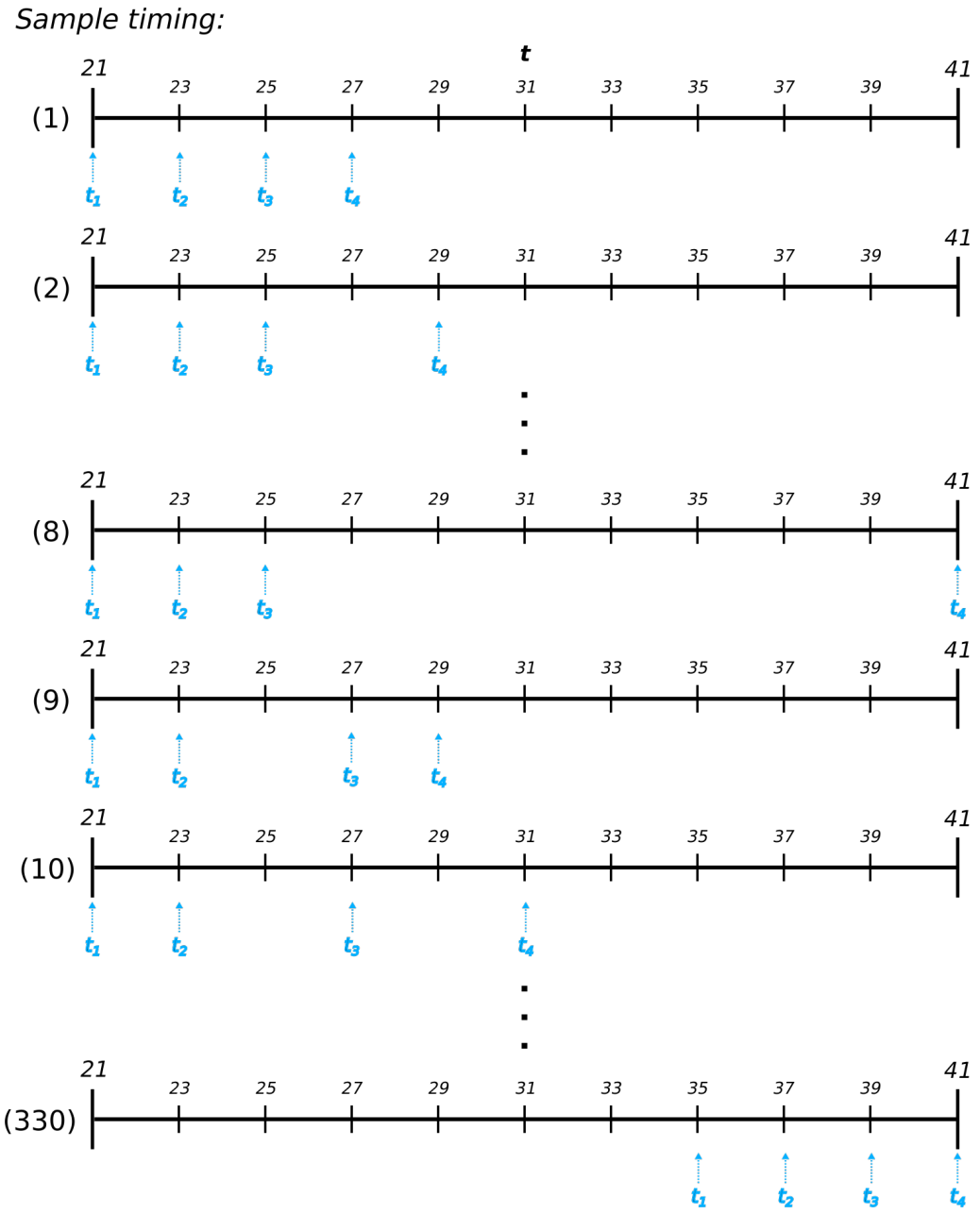


Figure 4.11: **Visualisation of method for varying the timing of four cross-sectional samples.** In order to analyse the effect of sample timing on the outcome of control and monitoring, we vary the timing of samples between $t_0 = 21$ and $t^* = 42$. Assuming four samples of equal size, we allow samples to be taken every second day, starting at $t_0 = 21$. We analyse every combination of four sample times from these possible days, giving a total of 330 different sample timings. They are ordered so that the final sample changes first, followed by the third sample, then the second and finally the first.

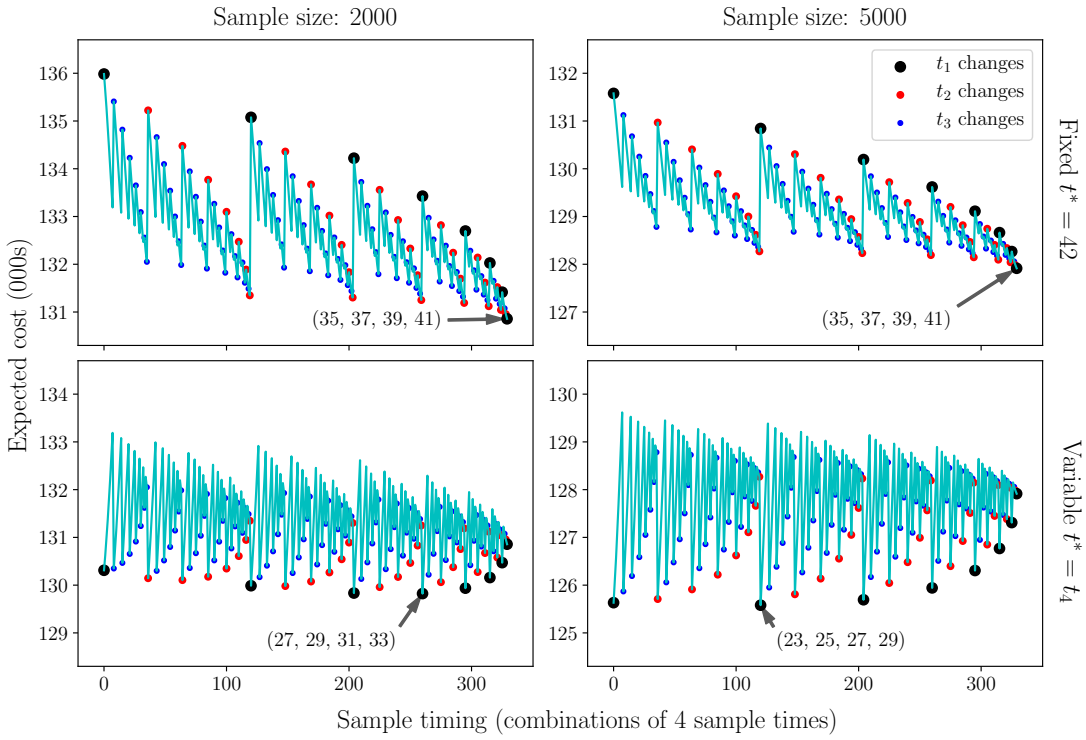


Figure 4.12: **Effect of sample timing on the expected cost of each initial decision not to vaccinate.** We vary the timing of four equally sized samples by taking all combinations of sample times on every second day for $21 \leq t \leq 41$ (see Figure 4.11 for a visual explanation). For each set of sample times, we calculate the expected cost of an initial decision not to vaccinate. We do so under two assumptions: 1) the final decision point is fixed at $t^* = 42$ (top row), and 2) the final decision is made immediately after the final sample is taken ($t^* = t_4$; bottom row). We also test two sample sizes: 2000 and 5000 individuals per sample (columns). The points at which the first three sample times change are idenitified with dots: the later samples change first and earlier samples last. The timing that gives the lowest expected cost is identified in each plot. The parameter values used are given in Table 4.1.

For a sample size of 2000, by taking samples on days $\{27, 29, 31, 33\}$ and making a final decision immediately after the last sample, we reduce the expected cost of an initial decision to wait by almost 2% compared to taking samples evenly spaced between days 21 and 42. Similarly, with a sample size of 5000, taking samples on days $\{23, 25, 27, 29\}$ reduces the expected cost by over 2.5%.

Overall, we find that sample timing can play a significant role in the efficacy of monitoring and our ability to resolve uncertainty, and hence significantly affects the expected cost of our decisions. From our three methods of uncertainty resolution, the mechanistic method is the only one that can reliably take this into account and optimise the timing of monitoring and control. Using this method in conjunction

with active AM could lead to significant reductions in the expected cost of the outbreak, up to 2.5% in the scenarios we tested.

Multiple decision points

We make one final adaptation to our procedure of monitoring and control, to further improve the expected cost arising from an initial decision not to vaccinate. Whilst we have shown that we can optimise the time of t^*, we now include the effect of allowing multiple times at which we can start vaccination. We do so using the mechanistic method of uncertainty resolution, based on the following observation: although we require 4 sample points to obtain an accurate posterior, we know that, unless β is very high, we will only make a final decision not to vaccinate if we do not observe any infections across all samples. As a result, as soon as we observe a single infection in the population, within any of the samples, it makes sense to begin vaccination immediately, thereby maximising the efficacy of the campaign. Hence, we will allow control decisions to be made on any of the sample days: after each sample, we can choose to begin vaccination, if we observe at least one infection in that sample, else continue without vaccination until the next sample is taken. We also assume that, if vaccination is started on one of the earlier sample days, it will not be stopped again after all samples have been taken even if it turns out that β is in fact very high, as we believe this would be more easily justifiable in real life. We summarise this method and detail the calculation of expected cost in Box 4.

By implementing multiple decision points, under our original conditions (4 samples of 2000 individuals evenly spaced between $t_0 = 21$ and $t^* = 42$), we find that we can reduce the expected cost of an initial decision to wait by 4%. This shows that the ability to start a campaign as soon as we know that $\beta > 0.2$ outweighs the benefit of learning whether $\beta > 0.55$ and not vaccinating if it is.

Box 4: Multiple decision points

In this box we summarise the method used to allow multiple decision points during the monitoring portion of the outbreak. Following the mechanistic method of uncertainty resolution, we take C cross-sectional samples of the population at times $\{t_i : t_0 \leq t \leq t^*\}$, containing M_i individuals each. The number of infections detected in each sample is denoted d_i. We only consider the case where we have made an initial decision not to vaccinate. We then allow a decision point immediately after each sample: if any infections are detected ($d_i > 0$), begin vaccination and continue until the vaccine pool is depleted (resulting in campaign $\mathcal{V}_{t_i,t_{end}}$), else ($d_i = 0$) continue without vaccination until the next sample is taken, or the outbreak ends.

Calculation of expected cost

Given an initial decision (a_0) not to vaccinate, and epidemiological parameters ϕ_0, we know that the number of infections detected in each sample, d_i, follows a *Binomial* distribution:

$$d_i \mid \phi_0 \sim \mathit{Binomial}\left(\frac{I(t_i)}{N(t_i)}, M_i\right) \tag{4.15}$$

The probability of starting vaccination at each decision point, and finally not vaccinating throughout, is calculated by the following set of equations:

$$\begin{aligned}
&P(d_1 > 0) = 1 - P(d_1 = 0)\\
&P(d_1 = 0, d_2 > 0) = P(d_1 = 0)(1 - P(d_2 = 0))\\
&\vdots\\
&P(d_1 = d_2 = \cdots = d_{t^*} = 0) = P(d_1 = 0)P(d_2 = 0)\ldots P(d_{t^*} = 0)
\end{aligned} \tag{4.16}$$

Hence, conditional on the parameter set ϕ_0, the expected cost of this initial decision is:

$$\begin{aligned}
C(a_0 \mid \phi_0) = {} & P(d_1 > 0)C(X \mid \mathcal{V}_{t_1,t_{end}}, \phi_0) + \\
& P(d_1 = 0, d_2 > 0)C(X \mid \mathcal{V}_{t_2,t_{end}}, \phi_0) + \\
& \cdots + P(d_1 = d_2 = \cdots = d_{t^*} = 0)C(X \mid \mathcal{V}_{0,0}, \phi_0)
\end{aligned} \tag{4.17}$$

Finally, as before, we integrate out the epidemiological parameters by their prior distribution $\pi(\phi_0)$, giving the expected cost of an initial decision not to vaccinate:

$$C(a_0) = \int_{\phi_0} C(a_0 \mid \phi_0)\pi(\phi_0)d\phi_0 \tag{4.18}$$

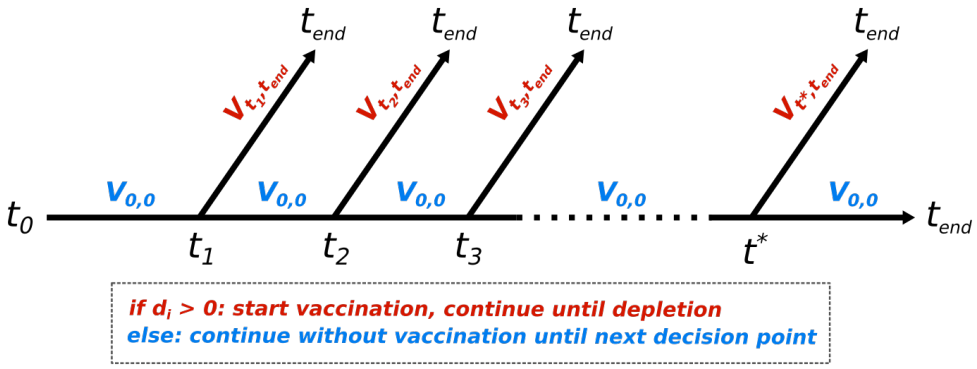


Figure 4.13: **Schematic of decision process allowing multiple opportunities to begin vaccination.** Under the mechanistic method of uncertainty resolution, we take C cross-sectional samples of the population at times t_1, t_2, ... , $t_C \leq t^*$. The number of infections detected in each sample is denoted d_i. When allowing multiple opportunities to begin vaccination, we assume that the initial decision (at t_0) is to not vaccinate. After each sample, if at least one infection is detected ($d_i \geq 1$), we will choose to implement a vaccination campaign from that day, continuing until the vaccine pool is depleted (resulting in vaccination campaign $\mathcal{V}_{t_i,t_{end}}$). Otherwise ($d_i = 0$), continue without vaccination to the next decision point. If no infections are detected from all samples, no vaccination campaign will be implemented for the entirety of the outbreak ($\mathcal{V}_{0,0}$).

Allowing multiple decision points also has significant effects on the optimisation of monitoring and control. For sample timing (Figure 4.14), we now find that it is beneficial to spread our samples out, having the first sample early and subsequent samples much later. In fact, if we allow the final sample to extend past $t = 42$, we find that it is optimal to push the final sample as late as $t = 81$, whilst keeping the first as early as possible. Hence, having the samples spread over a very wide range has become optimal, where before we chose to have them close together. For high values of β, where prevalence may already be high at early decision points, this allows us to take advantage of a quickly implemented campaign. However, when β is lower, therefore making infections more difficult to detect at early stages, it also allows time to resolve uncertainty and implement a campaign later on if necessary. Overall, for a sample size of 2000, taking samples on days $\{21, 29, 51, 81\}$ and allowing vaccination to begin as soon as a single infection is detected, reduces the expected cost of an initial decision to vaccinate by over 6%, compared to samples taken at evenly spaced intervals and $t^* = 42$.

For the optimal distribution of resources across samples, with only a single future decision point, we saw that having as much of the total sampling resources as possible on the final sample point was optimal (Figure 4.9). If we allow multiple decision points (Figure 4.15), whilst we should still assign the most resources to the final

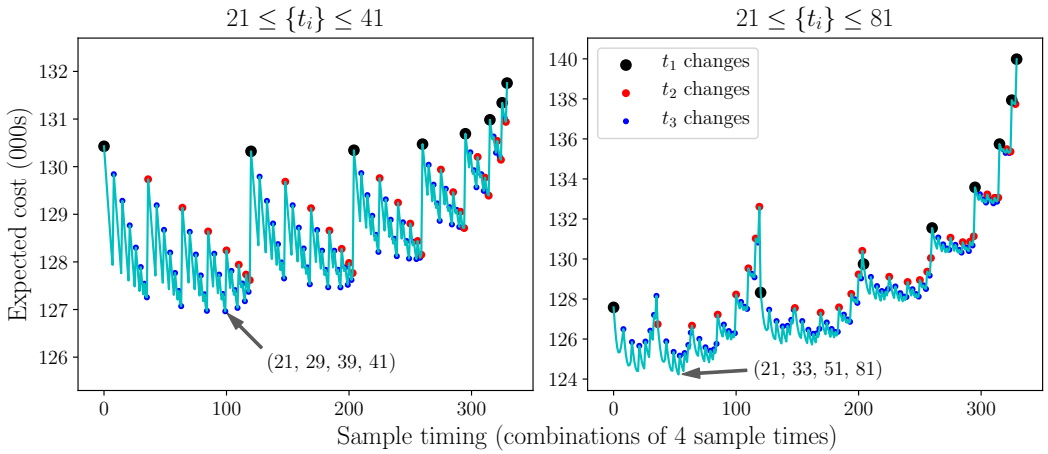


Figure 4.14: **Effect of sample timing on the expected cost of an initial decision not to vaccinate, allowing multiple opportunities begin vaccination.** We vary the timing of four equally sized samples of 2000 individuals each. Left: we analyse all combinations of sample times on every second day for $21 \leq t \leq 41$ (see Figure 4.11 for a visual explanation). Right: we analyse all combinations of sample times on every sixth day for $21 \leq t \leq 81$. For each set of sample times, we calculate the expected cost of an initial decision not to vaccinate, assuming that a decision to start vaccinating can be made immediately after any sample is taken and the final decision point is immediately after the last sample. The points at which the first three sample times change are identified with dots: the later samples change first and earlier samples last. The timing that gives the lowest expected cost is identified in each plot. The parameter values used are given in Table 4.1.

sample point, it is optimal to have more resources across the other samples compared to previously, since they have significantly more effect on our decisions, and to have more on the earliest and latest samples than those between. Any allocation that gives more resources to the two samples in the middle than the first and last samples will worsen the efficacy of monitoring and control, even compared to a constant sample size. However, where previously it was necessary to enforce a minimum sample size in order to allocate enough resources to the earlier samples, this is no longer the case. This emphasises the increased importance that is now placed on all samples, since any sample alone can trigger a decision to begin vaccination. Given a total sample size of 8000, to be split across 4 samples taken at evenly spaced intervals between $t_0 = 21$ and $t^* = 42$, if we allocate approximately 1700 (21.25%) to the first sample, 1250 (15.625%) to the second, 1400 (17.5%) to the third and 3650 (45.625%) to the final sample, we achieve a 0.5% reduction in expected cost compared to a constant sample size. The optimal distribution and its benefit is consistent across a range of total sample sizes. However, we note that, as the samples become more spread out in time, as with the optimal timing found above ($\{t_i\} = \{21, 33, 51, 85\}$), this benefit is reduced until a constant sample size becomes optimal, since the loss from making the wrong decision at any sample point is magnified.

Overall, we have found that allowing vaccination to start as soon as an infection is detected greatly improves the expected cost of an initial decision not to vaccinate, up to 6% in the scenarios tested, even though we do not allow vaccination to be stopped if β turns out to be very high. However, it also has a large effect on the optimal timing and distribution of monitoring resources, hence a decision to allow multiple decision points must be made at the start of the outbreak, else we may be in danger of making suboptimal recommendations.

4.6 Multiple uncertainties

Although we have focused on only a single source of uncertainty in the transmission rate β, we can easily extend this methodology to include more than one uncertainty. In this last section, we explore the effect of having both the transmission rate β and recovery rate γ unknown.

4.6.1 Modelling uncertainty in γ

We use similar methods to model the uncertainty in γ and its resolution as we have throughout this chapter.

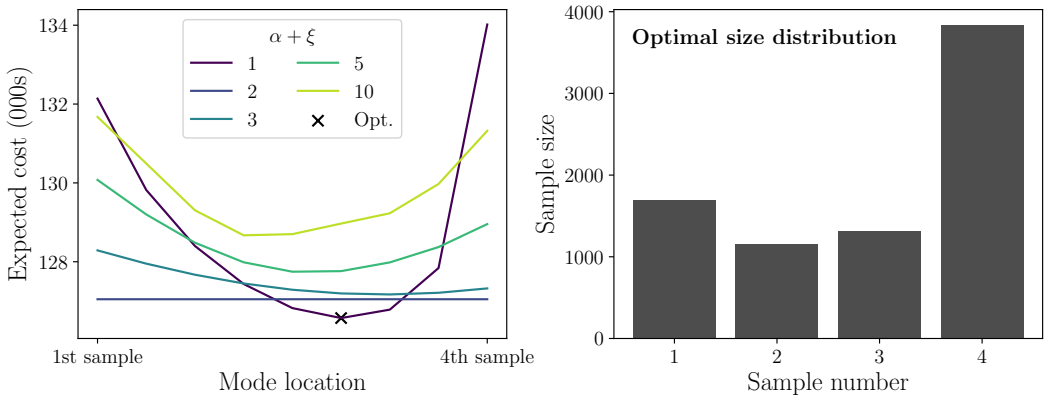


Figure 4.15: **Effect of sample size distribution on the expected cost of an initial decision not to vaccinate, allowing multiple opportunities to begin vaccination.** We vary the distribution of sampling resources across four samples using a $Beta(\alpha, \xi)$ distribution to split the total sample size $\left(\sum_{i=1}^{C} M_i = 8000\right)$ unevenly across the samples. We allocate $x_1 = F(0.25) \cdot \sum_{i=1}^{C} M_i$ to the first sample, $x_2 = (F(0.5) - F(0.25)) \cdot \sum_{i=1}^{C} M_i$ to the second sample etc, where F is the CDF of the *Beta* distribution. We vary both the location of the mode $\left(\frac{\alpha-1}{\alpha+\xi-2}\right)$ and the sum $\alpha + \xi$, providing a measure of how clustered around the mode the distribution is. The left-hand plot shows the expected cost of an initial decision not to vaccinate for a range of distributions, assuming that a decision to start vaccinating can be made immediately after any sample is taken and the final decision point is immediately after the last sample. The distribution that minimises the expected cost is identified with a black 'x'. The right-hand plots show the allocation of sampling resources across the four samples for the optimal distribution. The values of parameters used are given in Table 4.1.

First, we define the prior information using a $Beta(x, y)$ distribution, as described in Section 4.2.4, with mode = 0.2 and variance = 0.1. We can then model the resolution of uncertainty using each of our three methods:

Perfect information

We assume that all uncertainty in the recovery rate γ is resolved by the time we make our final decision at t^*. We do not necessarily assume that the uncertainty in β is resolved also. In order to quantify the benefit of resolving uncertainty in γ, but not β (or vice versa), we can use the Expected Value of Partial Perfect Information (EVPXI; Section 2.2):

$$\begin{aligned} EVPXI = \int_{\gamma} opt_{a_0,a_1} \left(\int_{\beta} C(X \mid a_0, a_1, \beta, \gamma)\pi(\beta)d\beta \right) \pi(\gamma)d\gamma \\ - opt_{a_0,a_1} \left(\int_{\beta,\gamma} C(X \mid a_0, a_1, \beta, \gamma)\pi(\beta, \gamma)d\beta d\gamma \right) \end{aligned} \tag{4.19}$$

Note, Eq 4.19 calculates the benefit of resolving uncertainty in γ and not β; we can easily calculate the converse by switching the parameters. However, as before, we edit this definition slightly to emphasise the fact that we are assuming perfect information at t^*, not immediately. We define the Expected Value of Future Perfect Partial Information (EVFPXI) to reflect this:

$$\begin{aligned} EVFPXI = opt_{a_0} \left(\int_{\gamma} opt_{a_1} \left(\int_{\beta} C(X \mid a_0, a_1, \beta, \gamma)\pi(\beta)d\beta \right) \pi(\gamma)d\gamma \right) \\ - opt_{a_0,a_1} \left(\int_{\beta,\gamma} C(X \mid a_0, a_1, \beta, \gamma)\pi(\beta, \gamma)d\beta d\gamma \right) \end{aligned} \tag{4.20}$$

Abstract resolution

We again use a mathematically convenient definition of the data and likelihood, that allows us to control the amount of uncertainty in γ that is resolved but is not linked to the state of the epidemic. We assume that real-time information is gathered via n observations of a process that follows a $Binomial(N, P)$ distribution with $N = 10$ and $P = \gamma$:

$$\text{Data: } \{z_i : 1 \leq i \leq n\}, \quad \text{Likelihood: } z_i \sim Binomial(10, \gamma) \tag{4.21}$$

Using the conjugacy of the *Beta* prior and *Binomial* likelihood, the posterior distribution of γ will be:

$$\textit{Posterior: } \gamma \mid \{z_i\} \sim \textit{Beta}\left(x + \sum_{i=1}^{n} z_i, y + 10n - \sum_{i=1}^{n} z_i\right) \tag{4.22}$$

Mechanistic resolution

We can incorporate an unknown γ into our existing fitting procedure without any changes to the set-up. We simply pass γ as an unknown parameter to be sampled over, initialising it in the `parameters` block, along with its prior distribution, defined in the `model` block, to our existing Stan programme.

4.6.2 Results

We perform the same procedure across all three definitions of uncertainty resolution and find that, under the priors we have used (Table 4.1), there is an even greater benefit obtained from performing active AM over a passive or non-AM approach when we introduce another uncertainty (Figure 4.16). Using the perfect information assumption, we can calculate the EVFPI metric (Equation 4.9), which increases to EVFPI = 15770, an almost 40% increase compared to when we only had a single source of uncertainty. These results are of course sensitive to the prior we place on γ: the kernel density plot in Figure 4.16 shows that there is significant uncertainty as to which campaign is optimal under these priors, however, if the prior on γ was centered higher, we may find that this uncertainty is reduced and the benefit of active AM over passive AM can become negligible.

The addition of further uncertainties will also affect the optimal monitoring and control parameters. For example, compared to the previous results, we may need to allow more resources and time to resolve uncertainty before we can be sure of the optimal final decision. This will affect the optimal timing of monitoring and control, causing an increase in optimal delays between initial and final decisions. However, the mechanistic method of uncertainty resolution, in conjunction with active AM, is already set up to handle such factors.

When we have multiple uncertainties, we may wish to analyse which are more important to resolve for optimising control, so that limited monitoring resources can be effectively targeted. If we assume perfect information at t^*, we can calculate the EVFPXI (Equation 4.20) for both parameters, showing the maximum benefit

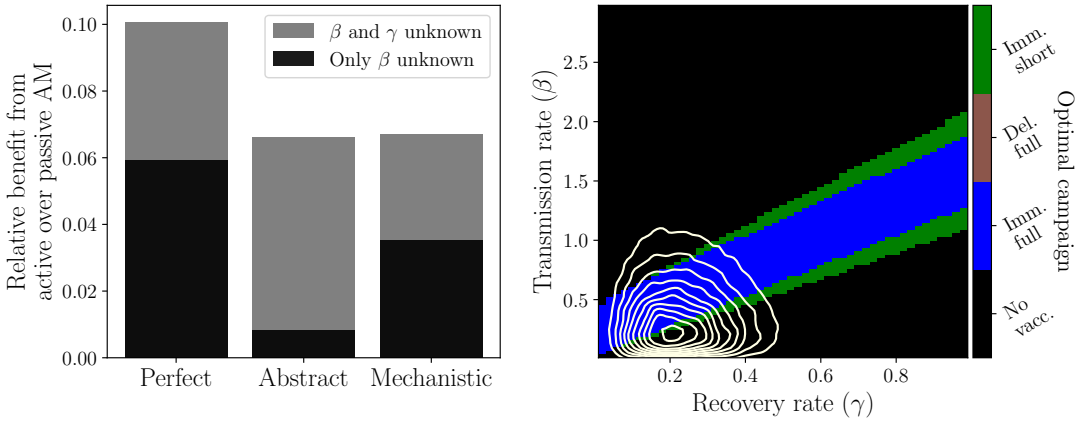


Figure 4.16: **Relative benefit of active AM over passive AM with both transmission (β) and recovery (γ) rates unknown.** We calculate the expected cost of the outbreak using active AM in conjunction with our three methods of uncertainty resolution (Boxes 1-3) and compare this to the expected cost under a passive AM approach, assuming that only β is unknown, as before, and both β and γ are unknown. Left: the relative benefit of an active AM approach compared to passive AM, for both scenarios and all methods of uncertainty resolution. For the abstract method, we assume 50 observations for each parameter. For the mechanistic method, we assume four samples of 5000 individuals each, taken on days $\{21, 28, 35, 42\}$. Right: optimal campaign for different true values of β and γ. The colour of each grid square represents the optimal campaign for that specific value of β and γ. The joint prior for β and γ is shown in white. Parameters used are given in Table 4.1.

obtainable from completely resolving β or γ individually. In this case, the EVFPXI from resolving β is 6953, whereas from γ is only 231. This suggests that, if a choice between resolving one or the other is necessary, resolving uncertainty in β is more effective for lowering the expected cost of the outbreak.

Using the abstract method of uncertainty resolution we can analyse the effect of partially resolving uncertainty in one or both of the parameters. If we vary the number of data observations for both β and γ and calculate the expected cost of each initial decision (Figure 4.17), we see that resolving uncertainty in β has much more of an effect on the expected cost than resolving uncertainty in γ, especially if β remains highly uncertain. This is what we would expect given our analysis of the EVFPXI. Translated into recommendations for an initial decision, resolving uncertainty in γ has almost no effect. If we assume that the resources required for observations of both parameters are equal, we can identify the optimal distribution of monitoring resources between the two parameters. At low levels of monitoring, we find it is better to allocate all monitoring resources to resolving uncertainty in β, as opposed to resolving both. For example, 20 data observations for β and none for γ results in a lower expected cost than 10 for each. At higher levels of monitoring, it is worthwhile allocating resources to resolving uncertainty in both parameters, but allocating more to β than γ can still improve outcomes. This analysis can therefore have a significant impact on recommendations for targeted monitoring. Although we have emphasised throughout that the abstract method of resolving uncertainty does not provide reliable recommendations, these results still provide important insight into how much uncertainty in each parameter needs to be resolved for it to have an effect on initial decisions.

Finally, we are unable to perform such analysis using the mechanistic method of uncertainty resolution, since we do not have specific monitoring for each unknown parameter and are therefore unable to separate the resolution of uncertainty between the two. However, this could easily be the situation we find in reality, therefore the analysis provided by the perfect information and abstract methods would also be rendered redundant in such contexts.

Overall, we have shown that the methods introduced in this chapter, especially the mechanistic method, can easily be extended to incorporate more than one source of uncertainty in the epidemiological parameters, and doing so may lead to even greater benefits from active AM compared to passive or non-AM approaches. We can also use the perfect information and abstract methods of uncertainty resolution to gain insight into which uncertainties are the most important to resolve for informing decisions, allowing targeted monitoring if necessary; however, any insights gained

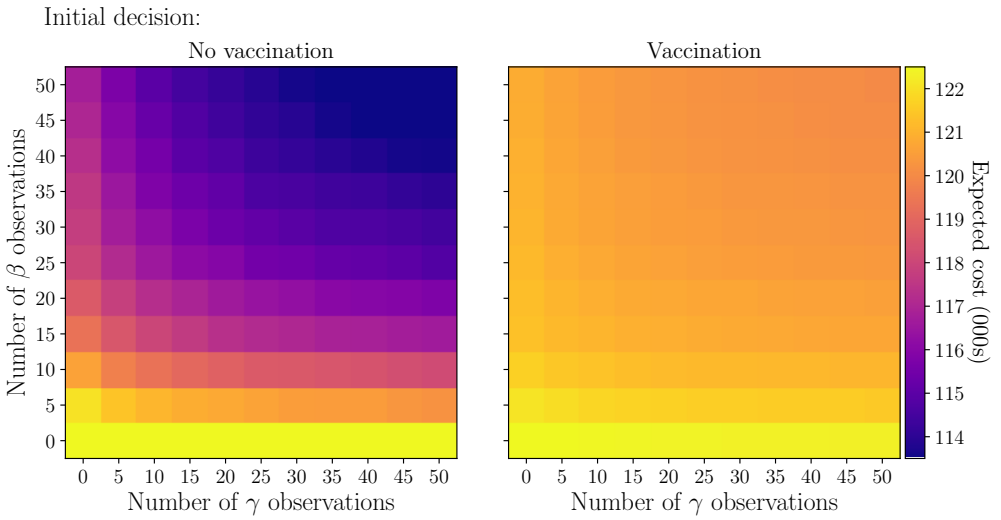


Figure 4.17: **Effect of the number of observations of β and γ on the expected cost of each initial decision.** We vary the number of observations of β and γ independently and calculate the expected cost of both initial decisions in each case (Algorithm 1). Observations are drawn from their respective likelihood distributions (Equations 4.11 and 4.21) and combined with their prior distributions to give posteriors based on Equations 4.12 and 4.22. The parameters used are given in Table 4.1.

from such methods should be interpreted carefully within the context of the outbreak.

4.7 Conclusions and discussion

In this chapter, we have analysed our ability to make an initial control decision in the face of uncertain epidemiological parameters. We followed an active AM approach to management, both predicting the effect of control actions and anticipating how the collection of real-time information may affect our future decisions. A major focus of this chapter was the method of modelling uncertainty resolution used within the active AM framework, that allows us to predict the effect that new information will have on the uncertainty in the system. We introduced three such methods: 1) assume that we have perfect information at future decision points, that is, all uncertainty will be resolved, 2) an abstract method of resolving uncertainty that relates to the unknown parameter but does not depend on the state of the epidemic, and 3) a mechanistic method that aims to directly model the relationship between the real-time information that is collected and the uncertainty in parameters. The first two methods have acted primarily as null models, emphasising the utility and necessity of the mechanistic method, but have also exhibited some functionality

themselves.

The first method of modelling uncertainty resolution, assuming that we will have perfect information when making the final decision, is unrealistic but also computationally unintensive and well used in the Value of Information literature (as EVPI; Section 2.2). As such, it is useful for quickly providing an upper bound on the benefit we may see from resolving uncertainty. If, even with perfect information, uncertainty resolution does not affect our current and future decisions, this would indicate that resources should not be allocated to monitoring if they can be used for control instead. However, if the opposite is true, further analysis into the effect of partially resolving uncertainty is necessary. If there is more than one source of uncertainty in the system, this method can also identify which of these lead to the greatest benefits when resolved, allowing effective targeting of monitoring and further analyses.

The second abstract method of modelling the resolution of uncertainty provides a convenient way to observe the effects of having 'more' or 'less' information. However, its detachment from the state of the epidemic itself makes it unreliable in accurately optimising control and monitoring and hence unsuitable for providing important insights. Whilst it is able to highlight the fact that a certain level of monitoring is required before an initial decision not to vaccinate becomes optimal over vaccinating immediately, the exact 'amount' required is not defined in real terms. Furthermore, whether or not it is feasible to collect this amount from the outbreak is not considered. Ignoring factors such as the difficulty of gathering accurate real-time information early on in an outbreak leads to underestimating the optimal delay between initial and final decisions, which ultimately leads to inflated outbreak costs. Finally, since this method does not involve a mechanistic model of the monitoring process, it does not allow for the optimisation of monitoring itself.

The final, mechanistic method of modelling uncertainty resolution, used in conjunction with the active AM framework, has proven to be an extremely useful tool in this scenario for making optimal initial decisions and also informing improved control and monitoring plans. By explicitly modelling the monitoring process and relating the information gained to the uncertainty in parameters directly, we can specify, in real terms, the amount of information required to properly inform decisions. We are also able to determine the optimal timing of monitoring, recognising the fact that monitoring resources may be relatively ineffective at the start of an outbreak compared to later. Although this method may involve computationally intensive, mathematically complex algorithms, it leads to significant reductions in the expected cost of the outbreak.

Using active AM and the mechanistic method of uncertainty resolution, we could make the following observations and recommendations to decision makers for the scenario we have used in this chapter: first, the amount of monitoring performed throughout the outbreak will have a significant effect on the expected cost of the epidemic, allowing reductions of up to 8% compared to relying on prior information alone. If we are able to test at least 4000 individuals in the population for the disease (across 4 samples) in the three weeks after disease detection, we would recommend not vaccinating until this monitoring has been performed. If any infections are detected within these samples, a vaccination campaign should be employed.

Whilst a minimum monitoring effort of 4000 individuals is necessary, the relationship between the amount of resources assigned to monitoring and the benefit obtained follows the law of diminishing returns. As such, it is necessary to estimate the cost of monitoring as accurately as possible, in order to avoid wasting resources on too much monitoring when they could be better used elsewhere. If the cost of monitoring is estimated to be very high, for example more than twice the cost of a vaccination, it would be better to forego monitoring and begin vaccinating immediately. However, if the monitoring cost is equal to the cost of vaccination, we recommend testing up to 16000 individuals in the population for the disease (across at least 4 samples). This capacity increases as the cost of monitoring falls.

If it is decided that we will not vaccinate immediately, but instead allow three weeks to monitor the epidemic before making a final decision, we can make several recommendations to maximise the benefit obtained. The monitoring resources should be split between at least four samples. Fewer, large samples are preferred to many, small samples, however, this will likely be restricted by the time taken to test a large number of individuals. If the final decision time is fixed at three weeks after detection, we would recommend taking all samples as close to the final decision as possible and allocating the majority of resources to the final sample. However, if it is plausible to have the final decision earlier, the samples should be taken earlier, though how much earlier depends on the size of the samples, with larger samples allowing for an earlier final decision.

If it is possible to start a vaccination campaign on any day in the three week monitoring period, we would recommend starting vaccination immediately after any sample that contains an infected individual and continuing until the vaccine pool is depleted. To obtain the most benefit from such an approach, samples should be spread out through the three week period, with the first occurring as early as possible and the last as late as possible, with the majority of resources allocated to the first and last samples. If it is acceptable to delay the final decision by more than

three weeks, we would recommend doing so, up to approximately two months, whilst keeping the first and last samples as early and late as possible, with other samples spread out between. In such a scenario, monitoring resources should be allocated equally to all samples.

As an example of the possible benefits, if we sample 8000 individuals in total across 4 samples on days $\{0, 12, 20, 60\}$ after the disease is detected and begin vaccination immediately if any infections are found (otherwise not vaccinating), we could reduce the expected cost of the outbreak by over 7% compared to taking a non-AM or passive AM approach. The recommended monitoring plan results in an almost 5% lower expected cost compared to taking 4 samples equally spaced in the three weeks after detection.

The analysis performed in this chapter highlights an important difference between active AM and experimentation. Although the control parameters themselves (e.g. vaccine efficacy) are assumed to be known, the overall effect of implementing that control is not, since it depends on the uncertain epidemiology of the disease. As such, even without experimentation, an active AM approach to management is highly important, since the resolution of uncertainty, whilst detached from the control itself, greatly affects the optimality of initial decisions. With active AM, we are able to recognise that some initial decisions enable us to make better use of real-time information in the future than others, which, as shown, results in better management.

To avoid monotony, we have not included sensitivity on the fixed parameters we used throughout this chapter. However, doing so reveals very similar results to the sensitivity performed in the previous chapter: the relative costs of vaccines (fixed and per vaccine) and infections can render the decision trivial, if one contributes significantly more to the overall cost than the other. Similarly, if the vaccination campaign is sufficiently large or small such that the uncertainty in epidemilogical parameters has little effect, or if the time to and probability of immunity from a vaccine is too low, initial decisions become trivial. Finally,if the R_0 of the disease is sufficiently high, vaccination becomes the obvious choice.

It is likely that many of the fixed parameters will also be unknown. We have shown in this chapter that including more uncertainties can strengthen the utility of active AM over passive or non-AM approaches. However, this assumes that the additional uncertainties can also be resolved to some extent through monitoring. In the next chapter, we give an example of how an additional uncertainty, without the possibility of resolving it, can diminish the benefits of resolving uncertainty in other parameters. However, as previously mentioned, it is necessary to adopt an active AM

approach even if it is to simply determine that monitoring and uncertainty resolution will not be beneficial.

Alongside the use of fixed, non-specific parameters, there are other limitations of this work that arise from using a highly simplified scenario. For example, we assumed the existence of an immediate, perfectly accurate test for the infection, used for monitoring the prevalence of the disease. In reality, such tests would not be perfect, possibly resulting in both false positives and negatives. Hence, to more accurately model the resolution of uncertainty, the sensitivity and specificity of such tests should be taken into account. Furthermore, the time taken to obtain a result from the test should also be incorporated.

Finally, we again assume that the disease follows a deterministic system of ODEs (Equation 4.1) with fixed parameters. In reality, the dynamics of the disease may be significantly more stochastic in nature, including the values of parameters such as transmission. Since our objective centred around the *expected* cost, as opposed to worst-case scenarios or time to elimination, we believe that the addition of such stochasticity would not have a large effect on the ranks of competing control measures. However, it could significantly impede our ability to resolve uncertainty, slowing the rate and restricting the total amount of uncertainty resolution. Thus, stochasticity would play an important role in the optimisation of control and monitoring. Models that capture stochasticity accurately are highly dependent on the context and require significant resources in both formulation and computation. Once a model has been developed, it can be incorporated into the AM framework in order to provide insights similar to those we have demonstrated in this chapter. However, a stochastic model requires many repeated runs, increasing the computational resources required significantly. Since the computational complexity of AM is already a barrier to its implementation, the benefits of including stochasticity would need to be carefully weighed against the approximations required elsewhere in the model, such as a discretised state space, limited control options and only few opportunities to adapt control.

In spite of these limitations, we believe the analysis in this chapter provides an important and relevant contribution to literature. The use of VoI measures such as the EVPI have been demonstrated to be beneficial in the management of epidemics [11, 126]. However, this work offers a valuable extension, clarifying the limitations of assumptions of perfect information and providing a mechanism to improve on such methods. We have also exhibited the ability to identify important uncertainties, those that, when resolved, provide the most significant improvements in management, using active AM, an area of increasing focus [10, 124, 126]. Finally,

we have shown how active AM can contribute to the effective planning and allocation of monitoring resources, an area that has been identified as extremely important for the management of epidemics [7, 15, 27].

Chapter 5

Risky behaviour and risk-averse management

Abstract

We introduce a more complex, Ebola-like disease model, and analyse the use of mass vaccination in the presence of 'risky behaviour': individuals that are vaccinated but do not gain immunity are less likely to seek healthcare if they develop symptoms than those that have not been vaccinated, thus making them more likely to spread the disease to others and die. We show that such behaviour can greatly reduce the effectiveness of a mass vaccination campaign in controlling the outbreak and, in extreme cases, cause an increase in the number of infections and deaths. We investigate the use of active AM to provide recommendations regarding the implementation of a mass vaccination campaign when both the vaccine efficacy and epidemiological parameters determining disease spread are unknown. We introduce mechanistic models to anticipate the resolution of uncertainty in these parameters and show how active AM can be used to find time- and state-dependent thresholds for the implementation of mass vaccination, restricting the probability of an undesirable outcome below a specified level.

5.1 Introduction

So far, we have focused on relatively simple scenarios in order to analyse in detail some of the elements of an AM approach to managing an epidemic. We have motivated the use of *active* AM in conjunction with mechanistic models of uncertainty resolution. In

this chapter we use these techniques in a more realistic setting and demonstrate our ability to extract useful and understandable information in the face of uncertainty.

We define a new model for resolving uncertainty in vaccine efficacy, based on a similar model for Ebola [144]. We stress here that, whilst this model is based on Ebola dynamics and control, we analyse it in a simplified, hypothetical scenario. Thus, we are not making recommendations regarding the control of Ebola outbreaks in the future, or assessing the control of previous outbreaks. The model incorporates the use of both a mass vaccination campaign and the establishment of healthcare centres as possible forms of control. We introduce the idea of 'risky behaviour', by assuming that people who are vaccinated are less likely seek healthcare if they present with disease symptoms than those who are not vaccinated [145]. We show that this can cause unexpected, and undesirable, outcomes from a mass vaccination campaign if vaccine efficacy is low, increasing the number of deaths in extreme cases. We incorporate multiple sources of uncertainty in both the control and epidemiological parameters.

We propose a more realistic management objective that relates to the risk-averse nature of decision makers. The primary objective of control is to minimise the total number of deaths caused by the outbreak. However, in contrast to previous chapters, we do not simply wish to minimise the expected number of deaths. Rather, given the possibility of increasing the number of deaths through a mass vaccination campaign, we require that the probability of increasing the total number of deaths remains below a specified value, ϵ. In order to do so, we use active AM to identify vaccine efficacy 'thresholds'. If an estimate of efficacy is above the required threshold, this triggers the implementation of a mass vaccination campaign. We show that active AM can be used to identify: static thresholds at a fixed point in time, dynamic thresholds that change with time and finally dynamic thresholds that depend on both time and the state of the epidemic. This requires the formulation of mechanistic models of uncertainty resolution, for both the vaccine efficacy and unknown epidemiological parameters.

Finally, throughout this chapter we demonstrate how multiple uncertainties can interact with each other, specifically the uncertainty in vaccine efficacy and transmission rate. We observe that, in extreme cases, the existence of a large amount of uncertainty in the transmission rate can render resolution of uncertainty in vaccine efficacy redundant. Even if the uncertainty in the transmission rate is not so great, it can significantly alter the amount of time required to sufficiently reduce uncertainty in the vaccine efficacy, affecting control and monitoring recommendations. Furthermore, if we also plan to resolve uncertainty in the transmission rate through monitoring,

the resolution of uncertainty in vaccine efficacy is affected by measurements of the transmission rate, even if the real-time information regarding vaccine efficacy remains the same. This highlights the necessity to understand and model the resolution of uncertainty in both parameters together in order to optimise monitoring and control.

5.2 An Ebola-like disease model

5.2.1 Model specification

We introduce a model that combines a simple, deterministic SEIR model of Ebola transmission (adapted from [144]) with two forms of control: the establishment of a specialised healthcare centre for infected individuals (such as an Ebola Treatment Centre [144]) and a mass vaccination campaign. We assume that the healthcare centre is established immediately after the disease is detected in the population, occurring once the outbreak reaches a certain level. A proportion of individuals who develop symptoms will seek healthcare (with healthcare-seeking probability h), whilst the remainder will not. If healthcare is sought, the individual remains in the community before being admitted to the healthcare centre (at rate κ), where they are isolated from the community, preventing onwards transmission, and treated, reducing the probability of dying from the disease. In the healthcare centre, they either recover, or die (with probability c_H) at rate γ, after which they are no longer infectious. If healthcare is not sought, the individual remains in the community, transmitting the disease to others, until they recover, or die (with probability $c \geq c_H$), at the same rate γ. After death, they remain infectious (possibly with increased infectiousness, ω) to the community until they have been buried (buried at rate α).

A mass vaccination campaign may also be implemented, however if and when remain part of the decision to be made. If it is decided to implement a mass vaccination campaign, individuals are vaccinated at a rate of ν_r per day, until the vaccine pool (ν_{pool}) is depleted. We assume imperfect targeting of the vaccine, delivered proportionally to both susceptible (S) and exposed (E) individuals. If an exposed individual is vaccinated, we assume it is completely ineffective and they remain in the incubation phase (V_E). If a susceptible individual is vaccinated, it will be effective with probability v_e (V_1). This leads to full, indefinite immunity, after a delay ν_d. Else, the vaccine is ineffective and the individual remains fully susceptible (V_0), however will not be considered for vaccination again. Finally, if an individual is vaccinated but develops symptoms, they will seek healthcare with probability h_v, possibly lower compared to the probability h for unvaccinated individuals. This

constitutes the 'risky' behaviour of vaccinated individuals.

The differential equations for the system are stated in Equation 5.1 and a schematic of the system can be found in Figure 5.1. The time dependence of state values has been excluded for brevity.

$$
\begin{aligned}
\frac{dS}{dt} &= \frac{-\beta S}{N}(I_H + I_C + \omega D_C) - \nu_r \left(\frac{S}{S+E}\right) \\
\frac{dE}{dt} &= \frac{\beta S}{N}(I_H + I_C + \omega D_C) - \sigma E - \nu_r \left(\frac{E}{S+E}\right) \\
\frac{dI_H}{dt} &= \sigma(hE + h_v V_E) - (\kappa + \gamma) I_H \\
\frac{dH}{dt} &= \kappa I_H - \gamma H \\
\frac{dD_H}{dt} &= \gamma(c_H H + c I_H) \\
\frac{dI_C}{dt} &= \sigma((1-h)E + (1-h_v)V_E) - \gamma I_C \\
\frac{dD_C}{dt} &= \gamma c I_C - \alpha D_C \\
\frac{dB_C}{dt} &= \alpha D_C \\
\frac{dR}{dt} &= \gamma \left((1-c_H)H + (1-c)I_H + (1-c)I_C + \frac{V_1}{\nu_d}\right) \\
\frac{dV_0}{dt} &= (1-\nu_e)\nu_r \left(\frac{S}{S+E}\right) - \frac{\beta V_0}{N}(I_H + I_C + \omega D_C) \\
\frac{dV_1}{dt} &= \nu_e \nu_r \left(\frac{S}{S+E}\right) - \frac{\beta V_1}{N}(I_H + I_C + \omega D_C) - \frac{V_1}{\nu_d} \\
\frac{dV_E}{dt} &= \nu_r \left(\frac{E}{S+E}\right) + \frac{\beta(V_0 + V_1)}{N}(I_H + I_C + \omega D_C) - \sigma V_E
\end{aligned}
\tag{5.1}
$$

We define a vaccination campaign in the same way as in the previous chapters: $\mathcal{V}_{t_i,t_j}$ representing a campaign that starts on day t_i and ends on day t_j. If $t_i \leq t \leq t_j$, the campaign is ongoing and

$$
\nu_r(t) = \begin{cases}
\nu_r, & \text{if } S(t) + E(t) \geq \nu_r, \\
S(t) + E(t), & \text{if } 0 \leq S(t) + E(t) < \nu_r, \\
\nu_{pool} - \int_{t_i}^{t} \nu_r(s)\mathrm{d}s, & \text{if } \nu_{pool} - \int_{t_i}^{t} \nu_r(s)\mathrm{d}s < \nu_r, \\
0, & \text{if } \int_{t_i}^{t} \nu_r(s)\mathrm{d}s > \nu_{pool}.
\end{cases}
\tag{5.2}
$$

If $t < t_i$ or $t > t_j$, the campaign is not currently ongoing and $\nu_r(t) = 0$. If no

vaccination occurs throughout the epidemic, we denote this by $\mathcal{V}_{0,0}$.

We assume that the outbreak occurs in a population of 500,000 individuals, starting with a single infected individual and is detected ($t = t_0$) once a total of 5 individuals have become symptomatic. The outbreak ends once the number of exposed (both vaccinated and unvaccinated) and infectious individuals (within the community and healthcare centres) together falls below 1 ($E(t) + V_E(t) + I_H(t) + I_C(t) + D_C(t) < 1$), denoted t_{end}.

5.2.2 Model behaviour

We explore the behaviour of this model for a range of different epidemiological and control parameters, before applying it within the AM framework. We focus on how these parameters affect the total number of deaths and infections caused by the disease outbreak. Parameters are varied unilaterally, with all other parameters fixed at their default values, given in Table 5.1.

Epidemiological parameters

Unsurprisingly, the epidemiological parameters have a significant effect on the outcome of the epidemic, due to their effect on R_0 (Figure 5.2). The R_0 of the epidemic without vaccination is estimated using Equation 5.3, adapted from [144]:

$$R_0 = h\left(\frac{\beta}{\gamma + \kappa}\right) + (1 - h)\left(\frac{\beta}{\gamma} + c\frac{\omega\beta}{\alpha}\right). \tag{5.3}$$

The first term in the sum represents the R_0 of individuals who seek healthcare and the second term those who do not.

Intuitively, an increase in the transmission rate β and length of infectious period $1/\gamma$ will lead to an increased R_0 and thus increased infections and deaths and a faster epidemic (Figure 5.2). We also see that an increased case fatality ratio in the community, c, causes an increase in both the total number of deaths and infections, since individuals remain infectious between death and burial, rather than becoming immediately immune in the case of recovery. Similarly, an increase in the delay between death and burial $1/\alpha$ or the relative increase in post-mortem transmission, ω, will also increase the total number of deaths and infections.

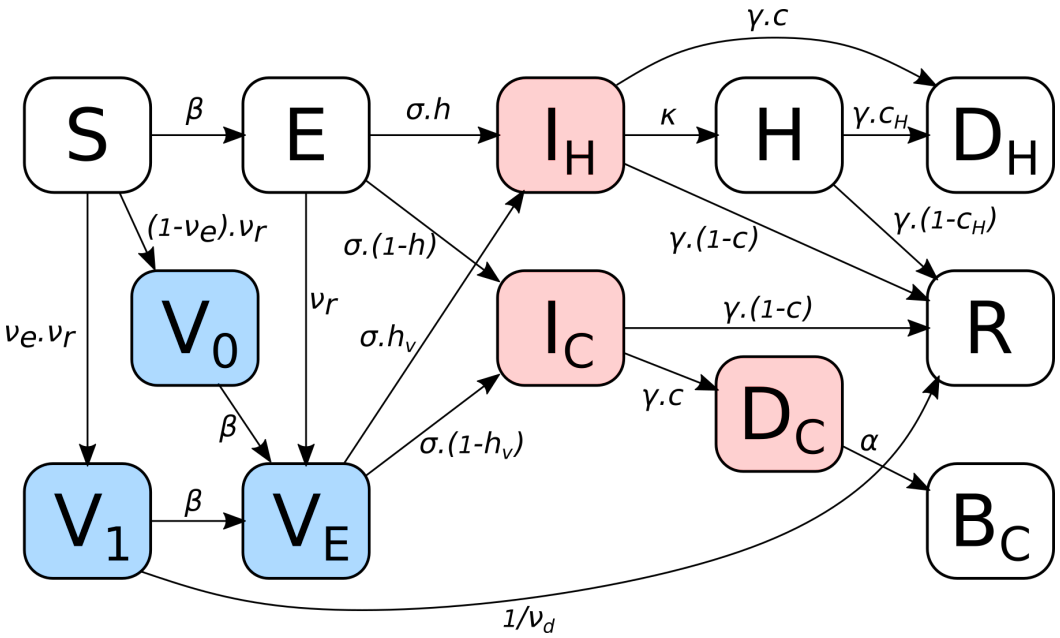


Figure 5.1: **Model of system behaviour.** We use a modified non-spatial, homogeneously mixing, deterministic Susceptible-Exposed-Infected-Removed (SEIR) model with vaccination and the establishment of healthcare centres as controls. The transmission (β), incubation (σ) and recovery (γ) rates are constant throughout the epidemic. A proportion of individuals who develop symptoms will seek healthcare (h and h_v for unvaccinated and vaccinated individuals respectively; move to I_H). If healthcare is sought, individuals are admitted to a healthcare centre at rate κ (move to H), where they are isolated from the community and treated. In the healthcare centre, they either recover (R), or die (with probability c_H; D_H) at rate γ, after which they are no longer infectious. If healthcare is not sought, the individual remains in the community until they recover (R) or die (with probability c; D_C). After death, they remain infectious (possibly with increased infectiousness, ω) until they have been buried at rate α (B_C). If vaccination campaign is active, individuals are vaccinated at a rate of ν_r per day, until the vaccine pool (ν_{pool}) is depleted. We assume imperfect targeting of the vaccine, delivered proportionally to both susceptible (S) and exposed (E) individuals. If an exposed individual is vaccinated, we assume it is completely ineffective and they remain in the incubation phase (V_E). If a susceptible individual is vaccinated, it will be effective with probability v_e (V_1). This leads to full, indefinite immunity (R), after a delay ν_d. Else, the vaccine is ineffective and the individual remains fully susceptible (V_0), however will not be considered for vaccination again.

Table 5.1: **Summary of parameters and notation used.** Default values apply throughout the chapter unless otherwise stated. Values left blank depend on the vaccination campaign and are calculated as required during the optimisation process. Where applicable, references for parameters are given in Ref. column. Parameters marked * have been chosen to give a realistic R_0 value [144] whilst allowing for non-trivial effects from a mass vaccination campaign.

Not.	Description	Value	Ref.
β	Transmission rate of disease	0.4	*
σ	Incubation rate of disease	1/9.4	[144]
γ	Removal rate from disease	1/7.8	[144]
κ	Hospital admission rate	1/2	[144]
α	Burial rate	1/7	[144]
h	Healthcare seeking rate	75%	*
h_v	Healthcare seeking rate if vaccinated	15%	*
c	Case fatality rate in community	70%	[146]
c_H	Case fatality rate in healthcare centre	35%	[146]
ω	Relative increase in transmission following death	1.5	*
ν_r	Daily vaccination rate (number of individuals)	1000	[33, 147]
ν_e	Vaccine efficacy	-	-
ν_{pool}	Total number of vaccines available	300000	[148]
ν_d	Delay between vaccination and immunity (days)	7	[147]
t_0	Detection and initial decision point (days after initial infection). Assumed to be the point at which a total of 5 individuals have become symptomatic	-	-
t^*	Final decision point (days after detection)	Various	-
t_{end}	Day on which outbreak ends (duration of the outbreak)	-	-
V_{t_i,t_j}	Denotes a vaccination campaign that starts on day t_i and ends on day t_j. We require $t_0 \leq t_i \leq t_j \leq t_{end}$	-	-
ϵ	Maximum allowable probability of increasing the number of deaths through vaccination	Various	-
N	Total population size	500000	-
R_0	Basic reproductive number of the outbreak, without vaccination, calculated via Equation 5.3	2	[36]

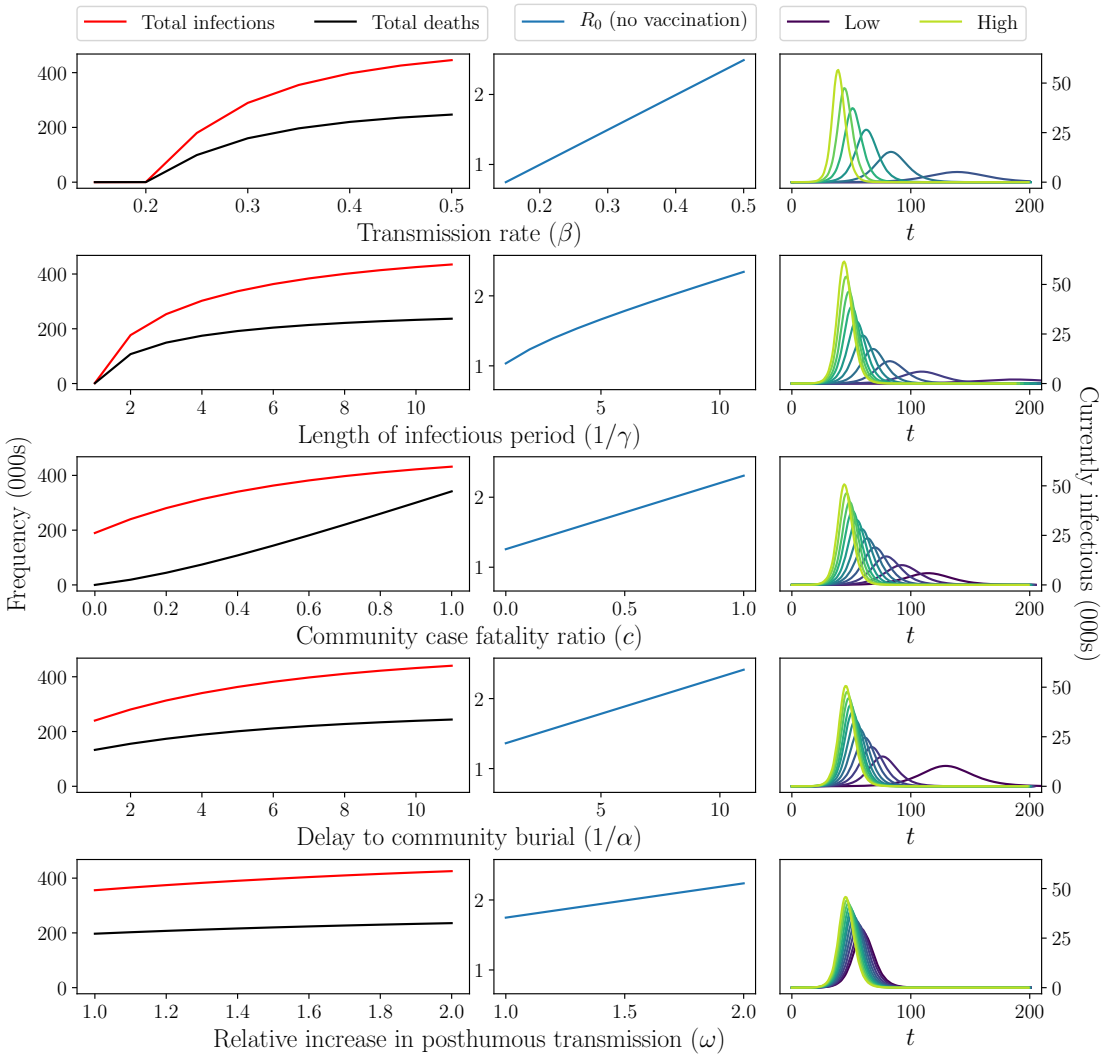


Figure 5.2: **Sensitivity to epidemiological parameters.** We vary the epidemiological parameters in the model, one at a time keeping other parameters fixed at their default values in Table 5.1. We do not include a mass vaccination campaign. We record the total number of infections and deaths (red and black; 1st column), the R_0 (blue; 2nd column) and resulting epidemic curves (multi-coloured; 3rd column).

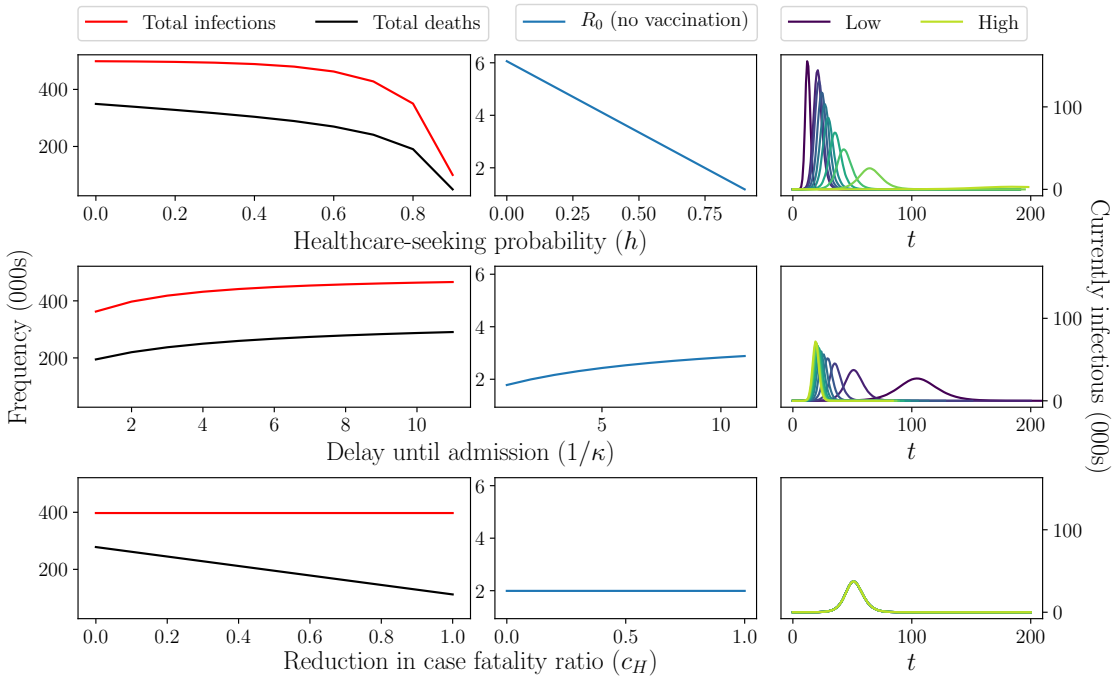


Figure 5.3: **Sensitivity to healthcare parameters.** We vary the parameters in the model relating to the healthcare centres, one at a time keeping other parameters fixed at their default values in Table 5.1. We do not include a mass vaccination campaign. We record the total number of infections and deaths (red and black; 1st column), the R_0 (blue; 2nd column) and resulting epidemic curves (multi-coloured; 3rd column).

Healthcare-seeking parameters

The healthcare-seeking probability h is also a primary component in the R_0 of the epidemic (Equation 5.3). Infected individuals that are admitted into healthcare centres can no longer infect others, and are guaranteed to have a safe burial. Thus, an increase in the healthcare-seeking probability will decrease the R_0 and the total number of infections and deaths (Figure 5.3). The time taken to be admitted into a healthcare centre after developing symptoms, $1/\kappa$, reduces the effectiveness of the centres to reduce infections. Hence, a longer delay leads to a higher R_0, more infections and more deaths. Finally, whilst the case fatality ratio c_H for individuals within healthcare centres does not affect the R_0 (since such individuals will not contribute to post-mortem transmission), a higher case fatality ratio will of course lead to more deaths, although the number of infections remains the same.

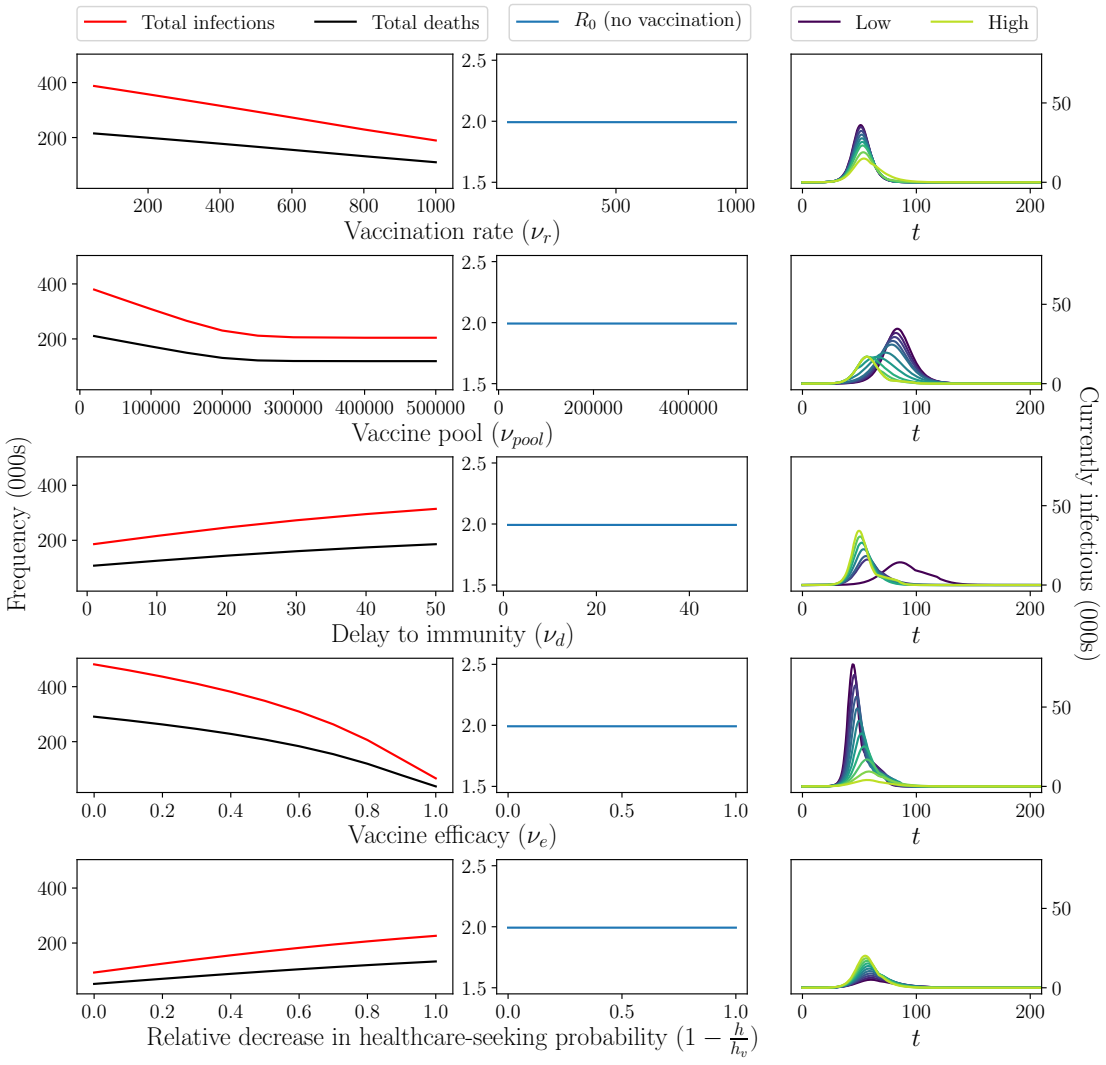


Figure 5.4: **Sensitivity to vaccination parameters.** We vary the parameters in the model relating to a mass vaccination campaign, one at a time keeping other parameters fixed at their default values in Table 5.1. We record the total number of infections and deaths (red and black; 1st column), the R_0 (blue; 2nd column) and resulting epidemic curves (multi-coloured; 3rd column).

Vaccination parameters

Finally, the effect of implementing a mass vaccination campaign depends heavily on the vaccination parameters (Figure 5.4). The larger and faster the campaign, the more effect it will have (both positive or negative - next section). A higher efficacy leads to fewer deaths and infections, however a lower healthcare seeking rate in vaccinated individuals can negate this if the vaccine is not 100% effective.

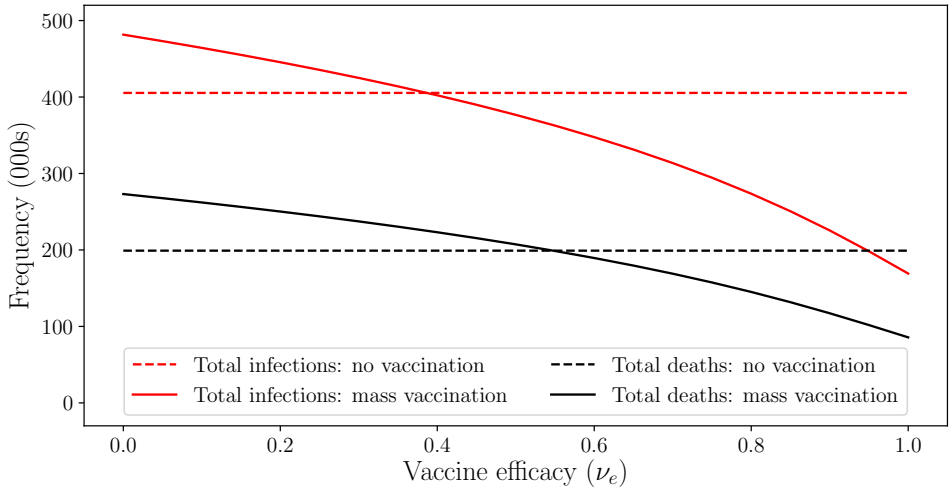


Figure 5.5: **Outcome of a mass vaccination campaign.** We record the total infections (red) and deaths (black) from the outbreak for a range of vaccine efficacy values, with (solid) and without (dashed) the implementaion of a mass vaccination campaign. Parameters are set to their default values, given in Table 5.1. The mass vaccination campaign is implemented on the day the disease is detected.

5.2.3 Effectiveness of mass vaccination

We saw in Figure 5.4 that the value of vaccine efficacy ν_e has a significant impact on the total number of infections and deaths caused by the disease. In fact, if the efficacy of the vaccine is low, we find that implementing a mass vaccination campaign can lead to an increased number of infections and deaths compared to not implementing the campaign (Figure 5.5). A low vaccine efficacy leads to an increased number of individuals who are vaccinated but become infected with the disease, resulting in more infections in the community due to a lower healthcare-seeking probability for such individuals. This is exacerbated by a higher case fatality ratio in the community compared to within healthcare centres and increased post-mortem transmission due to unsafe burials. In this example (Figure 5.5), if the vaccine is less than approximately 55% effective, a mass vaccination campaign will result in an increased number of deaths from the outbreak. The worst case scenario, if the vaccine is 0% effective, would be an almost 50% increase in the number of deaths. However, if the vaccine is highly effective, it could also reduce the number of deaths by up to 60%.

The possible negative effect of a mass vaccination campaign with low vaccine efficacy will depend on the other model parameters, especially the transmission and recovery rates (β and γ; Figure 5.6), the rate of healthcare-seeking in unvaccinated

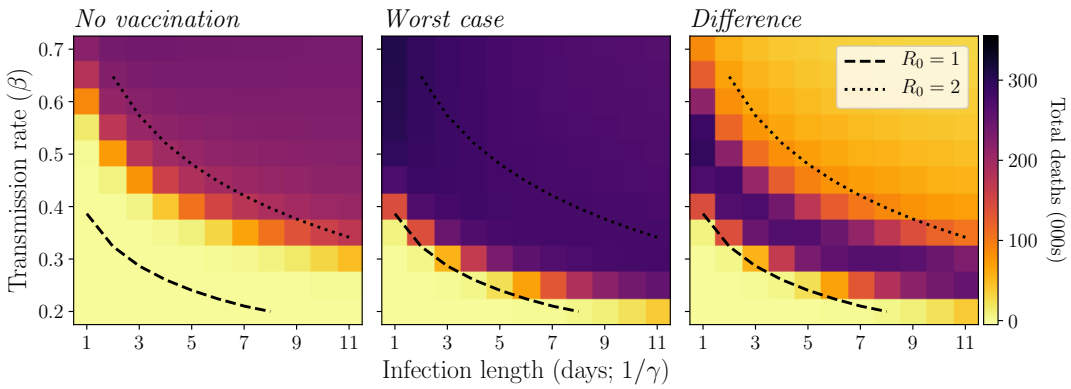


Figure 5.6: **Effect of epidemiological parameters on outcome of mass vaccination campaign.** We record the total number of deaths from the outbreak, for a range of β and γ values, assuming no vaccination (left) and the worst case scenario under a mass vaccination campaign (centre). The difference between the two is also shown (right). We highlight parameter values for which $R_0 = 1$ (dashed) and $R_0 = 2$ (dotted). All other parameters are set to their default values, given in Table 5.1. The mass vaccination campaign is implemented on the day the disease is detected.

and vaccinated individuals (h and h_v; Figure 5.7) and the speed, timing and size of the vaccination campaign (ν_r, t^* and ν_{pool}).

We find that the worst case scenario, from an ineffective vaccine, is most pronounced when $1 < R_0 < 2$, as within this range the vaccination campaign has the most effect on the transmission of the disease. Below this range, the disease quickly dies out with or without vaccination. As the R_0 increases above this range, the spread of the disease becomes so rapid that the vaccination campaign has relatively less effect, both in the best and worst case, due to the relatively slow roll out of the campaign (1000 per day) and delay to immunity. Whilst the transmission and recovery rates are major drivers of R_0 (Equation 5.3), other parameters in the model such as healthcare centre admission rate (κ), burial rate (α), post-mortem transmission (ω) and case fatality ratios (c and c_H) can also have a significant effect.

As the healthcare seeking rate for both unvaccinated (h) and vaccinated (h_v) individuals falls, the number of infections and deaths will increase (Figures 5.3 and 5.4). However, it is most detrimental to the outcome of a vaccination campaign if the healthcare seeking rate is high in unvaccinated individuals and low in vaccinated individuals (Figure 5.7). If the unvaccinated rate is low, the reduction caused by vaccination does not have a large effect on the total number of deaths. The sharp change in behaviour for $h \approx 0.9$ is caused by the effect of h on the R_0 of the epidemic (Equation 5.3), lowering it to below 1 without vaccination. However, the implementation of an ineffective vaccination campaign, with a significantly lowered

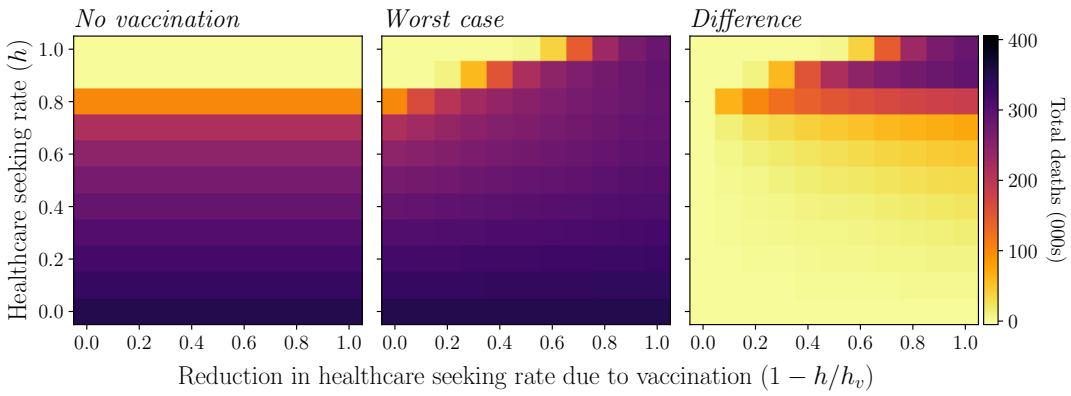


Figure 5.7: **Effect of healthcare-seeking behaviour on outcome of mass vaccination campaign.** We record the total number of deaths from the outbreak, for a range of h and h_v (represented as the relative reduction in healthcare-seeking: $1 - h/h_v$) values, assuming no vaccination (left) and the worst case scenario under a mass vaccination campaign (centre). The difference between the two is also shown (right). All other parameters are set to their default values, given in Table 5.1. The mass vaccination campaign is implemented on the day the disease is detected.

healthcare-seeking probability for vaccinated individuals, will reduce the proportion of infectious people seeking healthcare and thus raise the R_0 back above 1, causing a significant contrast in the outcome of the epidemic with and without vaccination.

Finally, the campaign itself has a significant, but intuitive, effect. The larger and faster the campaign (higher values of ν_{pool} and ν_r respectively), the more extreme the worst case scenario. Of course, the possible benefits of mass vaccination are also maximised, so there is greater disparity between the two. The later the start day of the campaign (t^*), the less effect the campaign has on the outcome. Hence, the worst case scenario is less extreme, but the benefits will also be less.

5.3 Estimating vaccine efficacy

We showed in the previous section that implementing a mass vaccination campaign can increase the total number of deaths from the outbreak, if vaccine efficacy is low and vaccinated individuals are less inclined to seek healthcare once symptoms develop. Part of our management objective is to keep the probability of this occuring below a specified value ϵ. Unless we have strong prior information regarding the efficacy of the vaccine, this may not be possible at the start of the outbreak. As such, under a non-AM approach to managing the outbreak, the use of a mass vaccination campaign would not be recommended. However, in this section, we introduce a

model for resolving uncertainty in the vaccine efficacy via a vaccine trial, performed on a small, isolated subset of the population during the early stages of the outbreak. Using the AM framework, we can optimise the vaccine trial and provide state- and time-dependent recommendations for the implementation of a mass vaccination campaign in the future, based on the estimate(s) of vaccine efficacy obtained from the trial.

5.3.1 Vaccine trial model

We assume that uncertainty in vaccine efficacy is resolved via a randomised controlled vaccine trial [149]. We model this using a simplified version of the disease model: disease dynamics follow an SEIR model with the same β, σ and γ parameters. We remove healthcare-seeking behaviour on the assumption that all individuals in the trial will be closely monitored and provided with healthcare if necessary [149]. We assume an isolated subsection of the population for the trial, in which disease levels are representative of the main population. From the trial population, 50% are immediately recruited into the vaccination group and 50% into the control group, although initial symptomatic infections are removed. Since individuals may already be exposed but asymptotic at the start of the trial, we do not include infections that occur within the first time period of incubation, in both control and vaccinated groups, in the estimates of efficacy.

An estimate of vaccine efficacy at time t is obtained by [145, 150]:

$$\hat{\nu_e}(t) = 1 - \frac{r_v(t)}{r_c(t)}, \quad \text{where} \quad \begin{aligned} r_v(t) &= \frac{\text{cases in vaccinated group at } t}{\text{total number vaccinated at } t} \\ r_c(t) &= \frac{\text{cases in control group at } t}{\text{total number of control at } t}. \end{aligned} \tag{5.4}$$

In order to introduce uncertainty into these estimates, we simulate the vaccine trial model using the Gillespie algorithm. By doing so, we can obtain an empirical distribution of estimates we would expect to obtain from a trial, conditioned on the true value of vaccine efficacy and other epidemiological parameters: $f(\hat{\nu_e} \mid \nu_e, \beta, \sigma, \gamma)$. We expect this distribution to converge on the true value of vaccine efficacy at later stages in the trial (Figure 5.8). We explore the accuracy of estimates in more detail in the next section.

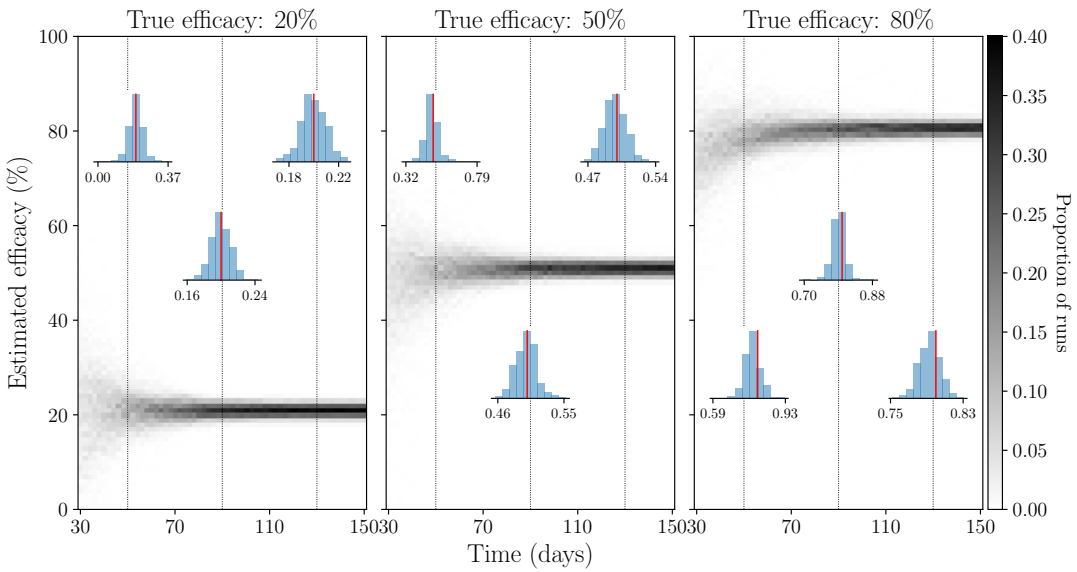


Figure 5.8: **Vaccine efficacy estimates from a vaccine trial.** We simulate the vaccine trial model 1000 times and calculate the estimate of vaccine efficacy each day for 150 days. Heatmaps show the density of estimates over time, for 3 true values of vaccine efficacy 20%, 50% and 80%. In each plot, histograms highlight the distribution of estimates at 3 points in time: $t = 50, 90, 130$ (days after detection). The trial is performed on a population of 2000 people. All other parameters are set to their default values, given in Table 5.1.

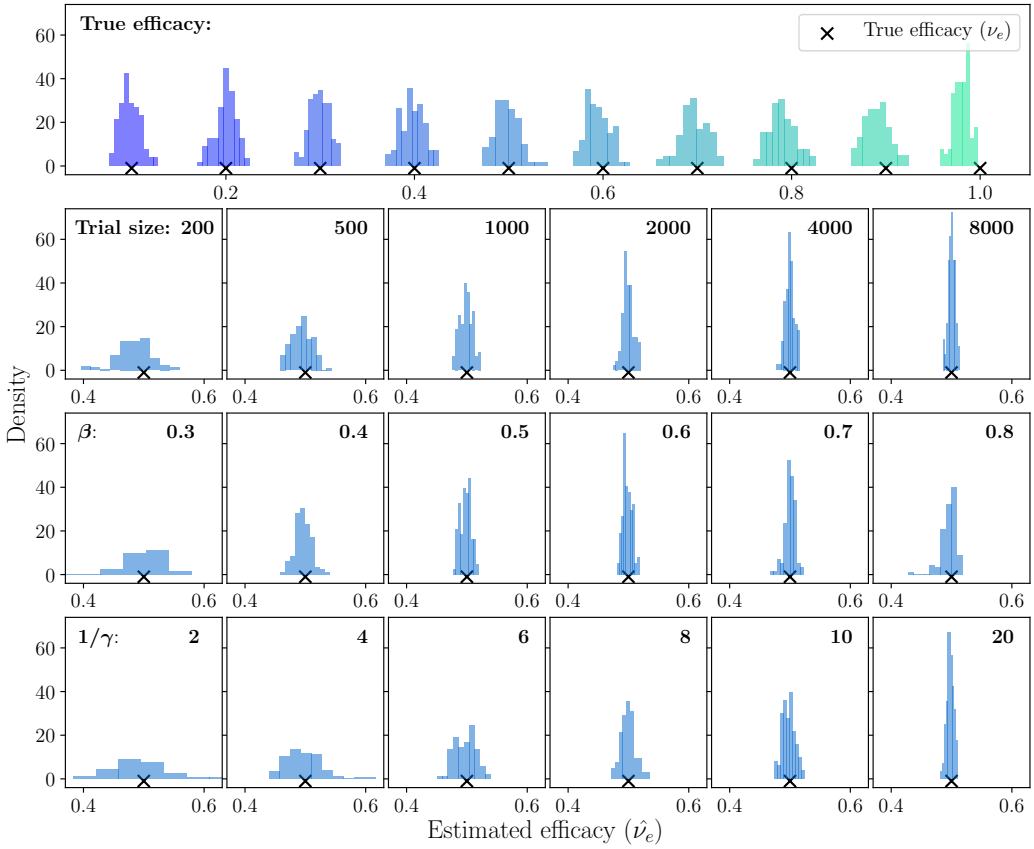


Figure 5.9: **Distributions of vaccine efficacy estimates.** We simulate the vaccine trial 100 times for a range of true vaccine efficacies, trial sizes, β and γ values. We present the distribution of vaccine estimates obtained on day 100 of each trial. Parameters are varied one at a time, with other parameters set to their default values, given in Table 5.1. The default vaccine efficacy is 50% and trial size 2000. Black crosses mark the true value of efficacy.

5.3.2 Behaviour of estimates

The distribution of estimates of vaccine efficacy ($f(\hat{\nu_e} \mid \nu_e, \beta, \sigma, \gamma)$) that we obtain from a vaccine trial are highly dependent on a number of factors, including the true value of efficacy, the length and size of the trial and the value of epidemiological parameters (Figure 5.9).

First, whether or not the mode of the distribution is centred around the correct value depends on the true value of efficacy (Figure 5.9; top row). As the true value of efficacy increases, the results from the vaccine trial begin to significantly underestimate the efficacy, due to the imperfect targeting of vaccines (that is, vaccinating already exposed individuals) and the lag between vaccination and immunity.

At lower levels of true efficacy, where the number of infections in both vaccinated and control groups is large, this will have little effect on the overall distribution of estimates. However, when the true efficacy is high, we expect very few infections in the vaccinated group and hence the effect is much greater. Whilst it is important to understand such sources of error, this will not impede our ability to use these estimates for posterior predictions of efficacy and control outcomes.

The timing and size of the trial also have a clear effect on the distribution of estimates. As the size (Figure 5.9; second row) or length (Figure 5.8) of the trial increases, the variance of the distribution decreases significantly. Note these parameters also interact with each other: a larger sample will resolve uncertainty faster than a smaller sample.

Finally, the epidemiological parameters affect the distribution of estimates through the R_0 of the epidemic (Figure 5.9; rows 3 and 4). As the R_0 increases, through an increased transmission rate (β) or infection length ($1/\gamma$), the disease will be more prominent in the trial populations and thus estimates will generally exhibit less variation. However, note that at high values of β, estimates will be more affected by the treatment of early infections mentioned previously. Hence, the distribution of estimates may become more skewed and begin to exhibit more variation.

5.3.3 Identifying threshold estimates

We first focus on our ability to inform management decisions based on the results of the vaccine trial, assuming that the transmission rate β is known. This allows us to clearly portray the mechanics behind the decision process, and how factors such as the length of the trial and the acceptable probability of increasing deaths (ϵ) affect the results.

True thresholds, estimated thresholds and opportunity cost

The minimum value of vaccine efficacy required to reduce the total number of deaths through a mass vaccination campaign, given all other parameter values, can be found using Equations 5.1. We name this value the true threshold. In order to recommend a mass vaccination campaign, we must be $(1-\epsilon)\%$ confident that the vaccine efficacy is above this value. The true threshold is highly dependent on the model parameters: in general, a lower R_0 or weaker vaccination campaign (slower or smaller) will result in a higher true threshold.

Given an estimate of efficacy $\hat{\nu_e}$, we can obtain a posterior distribution for the

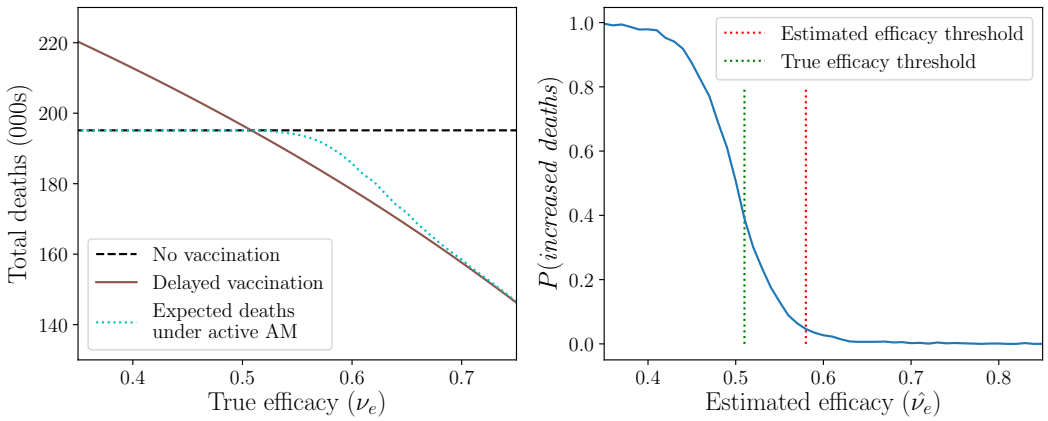


Figure 5.10: **Example outcome of decision process.** Left: the total number of deaths from no vaccination (black dashed) and a delayed, mass vaccination campaign (brown solid) for a range of true vaccine efficacy values. The blue dotted line shows the expected number of deaths under our active AM decision process, with $\epsilon = 0.05$ and $t^* = 50$. Right: the probability of increasing the total number of deaths through a mass vaccination campaign, for a range of vaccine efficacy estimates (solid blue line). Dotted green and red lines show the true and estimated thresholds respectively. Other parameters are set to their default values, given in Table 5.1.

true efficacy ν_e using Bayes Theorem:

$$f(\nu_e \mid \hat{\nu_e}) = \frac{f(\hat{\nu_e} \mid \nu_e)\pi(\nu_e)}{\int_{\nu_e} f(\hat{\nu_e} \mid \nu_e)\pi(\nu_e)d\nu_e}, \tag{5.5}$$

with prior $\pi(\nu_e)$ and likelihood $f(\hat{\nu_e} \mid \nu_e)$. We approximate the likelihood by simulating an empirical distribution for $\hat{\nu_e}$, using many observations of the vaccine trial process described previously and a discretized range of estimates. The integral in the denominator is approximated using Monte Carlo methods.

Using the posterior distribution for the true vaccine efficacy, $f(\nu_e \mid \hat{\nu_e})$, we are able to calculate the probability of a mass vaccination campaign increasing the total number of deaths as the proportion of the posterior distribution that is below the true threshold (the minimum efficacy required to decrease the total number of deaths through vaccination). We can then choose a threshold for the estimated efficacy, such that the probability of increasing the number of deaths is less than a chosen value ϵ (Figure 5.10; right-hand plot). We call this the estimated threshold. The estimated threshold will clearly be higher than the true threshold, given the remaining uncertainty in the posterior distribution. If we increase the size or length of the vaccine trial, we obtain thinner posteriors and hence the etimated threshold will decrease towards the true threshold.

By only implementing a mass vaccination campaign if the estimate of efficacy gained from the vaccine trial exceeds the estimated threshold, we guarantee that the probability of implementing an ineffective campaign, ultimately increasing the number of deaths, remains below ϵ. This means that, if the vaccine efficacy is below the true threshold, we will almost always make the correct decision not to implement a vaccination campaign (Figure 5.10; left-hand plot - dotted blue line agrees with dashed black line for low vaccine efficacy). However, on the other hand, if vaccine efficacy is above the true threshold, there is a significant chance of not vaccinating when it would in fact be optimal . This is most probable for values of efficacy that lie between the true and estimated thresholds, for which the estimate from the vaccine trial is likely to be lower than the estimated threshold, thus leading to a conclusion not to vaccinate (Figure 5.10; left-hand plot - dotted blue line disagrees with brown line for $0.55 < \nu_e < 0.7$). This may result in missing out on the opportunity to drastically reduce the number of deaths through an effective vaccination campaign. We refer to this as the opportunity cost. Throughout the remainder of this section, we focus on providing estimated thresholds to keep the probability of increasing deaths below ϵ, whilst also providing guidance on how to minimise the opportunity cost of not vaccinating, thus satisfying both aspects of the management objective.

Predetermined trial length

First, we assume that a single estimate of efficacy will be obtained from the vaccine trial, on a predetermined day in the future (t^*). However, determining t^*, the length of the vaccine trial, is part of our analysis and can be used to minimise the opportunity cost associated with the decision.

The maximum probability of increasing deaths allowed by decision makers, ϵ, will dictate if and when we should implement a mass vaccination campaign (Figure 5.11). The lower we require this probability to be, the more cautious we must be in implementing a campaign. As such, the threshold for the estimate of vaccine efficacy, above which we will vaccinate and below we will not, will increase as we decrease this probability. This has more of an effect for short vaccine trials, for which the estimates of efficacy are significantly less precise. Having a lower ϵ will also lead to a higher overall expected number of deaths, due to an increased opportunity cost of not vaccinating when a campaign is in fact effective. Again, this has a significantly greater effect for short vaccine trials compared to long.

The length of the vaccine trial itself plays a large part in determining the estimated threshold. Since longer trials provide more precise posterior estimates of vaccine

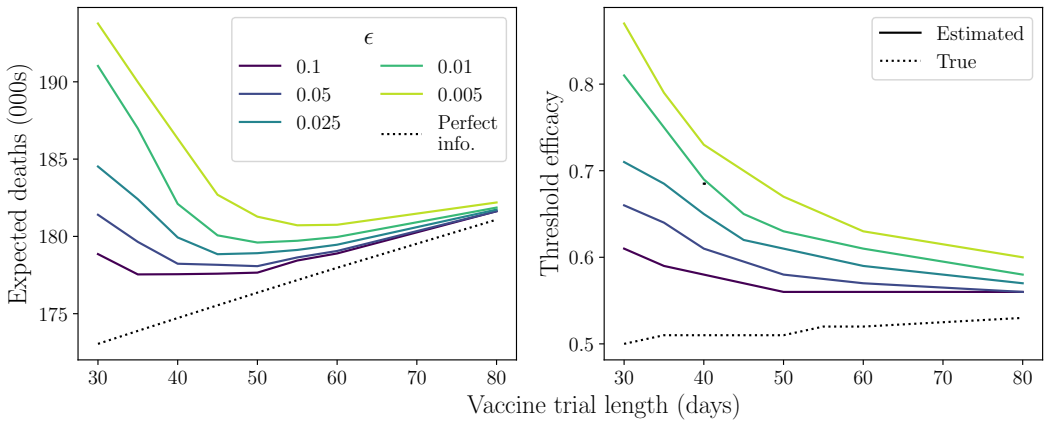


Figure 5.11: **Effect of vaccine trial length and ϵ on outcome and thresholds.** We calculate the expected number of deaths (left) and true and estimated vaccine efficacy thresholds (right; dotted and solid respectively) for a range of vaccine trial lengths (x-axis) and values of ϵ (colours). In the left-hand plot, the dotted line shows the expected number of deaths achievable with perfect information. Other parameters are set to their default values, given in Table 5.1.

efficacy, the estimated threshold will decrease towards the true threshold as the trial length increases and the expected number of deaths overall approaches what we would achieve with perfect information (Figure 5.11). Therefore, a longer trial will also decrease the opportunity cost. However, note that the true threshold efficacy also changes as we increase the length of the trial. Hence, if the vaccine trial is too long, the estimate of efficacy required to implement a campaign will begin to increase again. This is because a campaign that is implemented later in the outbreak requires a higher efficacy to reduce the number of deaths. Furthermore, such a campaign will have less of an impact on the outcome of the epidemic. As a result, there is a conflict between giving ourselves time to resolve uncertainty and not waiting too long to implement a campaign. If the vaccine trial is very short, the high variance of the posterior for vaccine efficacy demands a very high estimate to implement a campaign, therefore we will likely miss out on the opportunity to reduce the number of deaths with an effective campaign, even if vaccine efficacy is reasonably high. However, if the trial is too long, whilst the posterior for vaccine efficacy will be very precise, we will have missed out on the chance to implement an effective campaign earlier. Hence, there is an optimal vaccine trial length. The optimal length also depends on ϵ: if ϵ is very low, we require a longer trial than for larger ϵ, since we need more precise estimates to allow a vaccination campaign to be implemented. In the example shown in Figure 5.11, the optimal trial length ranges from 35 days for $\epsilon = 10\%$ to 55 days for $\epsilon = 0.5\%$.

The vaccine trial size has a similar effect to the length of the trial: a larger trial provides more precise estimates of vaccine efficacy, hence the estimate required to allow vaccination will be closer to the true threshold and the opportunity cost will decrease. As such, it is best to have as large a trial as possible. However, this comes with nontrivial considerations, such as the ability to follow up and provide care for all individuals involved in the trial, or the constraints on administering a large number of vaccines in a short period of time.

Time-dependent threshold

Next, we assume that we have the ability to take multiple estimates of efficacy from the vaccine trial over time. The value of each estimate can trigger the implementation of a mass vaccination campaign if it exceeds the time-dependent estimated threshold. We analyse a scenario in which estimates are obtained from the vaccine trials every ten days between day 30 and 80, inclusive (Figure 5.12). We find that, providing a time-dependent estimated threshold and implementing a mass vaccination campaign as soon as an estimate of efficacy exceeds this threshold further improves the expected outcome of the epidemic, compared to any vaccine trial with a predetermined length. This is because it encourages early implementation of campaigns when vaccine efficacy is very high, whilst allowing for a longer trial and thus further resolution of uncertainty if efficacy is lower, reducing the opportunity cost. The probability of starting a campaign after each estimate is taken depends on the value of ϵ (Figure 5.13). If $\epsilon = 10\%$, we are most likely to begin a campaign after the first estimate compared to subsequent estimates. However, if we decrease ϵ to 1%, we are unlikely to begin vaccination until the second estimate has been taken. This can help to inform how long we should keep taking estimates without implementing a campaign. For higher ϵ, it is very unlikely that we will obtain any estimates high enough to warrant implementing a campaign after 80 days into the vaccine trial. However, for lower ϵ, it may be worth continuing taking estimates after 80 days. If the vaccine trial itself has significant ongoing costs, it may be worth including another threshold at low estimates of efficacy, that could be used to prematurely stop a vaccine trial.

5.4 Estimating epidemiological parameters

We now consider a scenario in which both the vaccination and epidemiological parameters are unknown. We first introduce an unknown transmission rate and explore

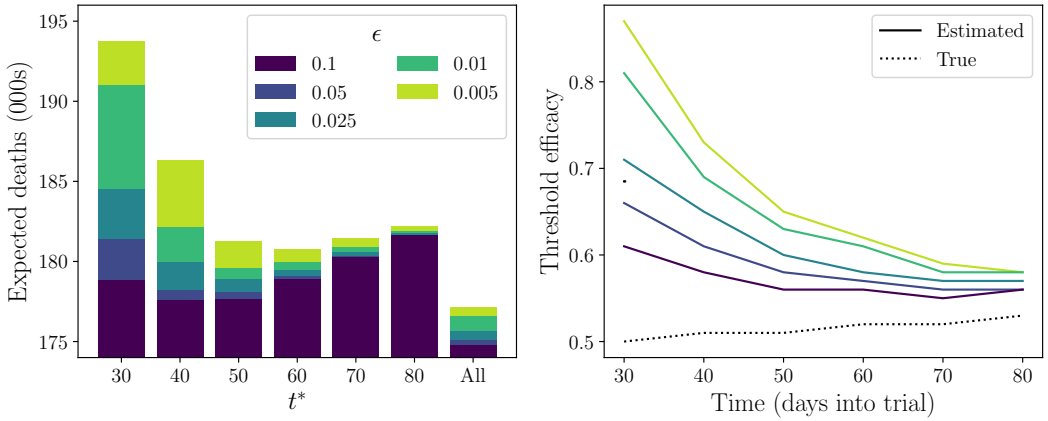


Figure 5.12: **Dynamic, time-dependent thresholds.** We calculate the expected number of deaths (left) and true and estimated vaccine efficacy thresholds (right; dotted and solid respectively) assuming multiple estimates of vaccine efficacy from a single trial, taken at 10 day intervals from 30 to 80 days after disease detection, for a range of values of ϵ (colours). In the left-hand plot, the expected number of deaths using a single estimate at different points in time is compared to the expected number of deaths using multiple estimates ('All'). Other parameters are set to their default values, given in Table 5.1.

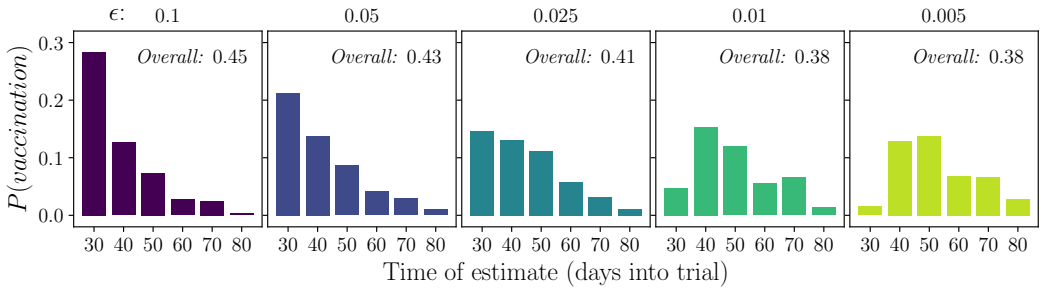


Figure 5.13: **Probability of implementing mass vaccination campaign over time.** Using the dynamic, time-dependent thresholds calculated in Figure 5.12, we calculate the probability of implementing a mass vaccination campaign after each estimate, for estimates taken every 10 days between 30 and 80 days after disease detection. We do so for a range of values of ϵ. Other parameters are set to their default values, given in Table 5.1.

the effect it has on our estimated threshold. We then incorporate a 'measurement' of the transmission rate taken during the early stages of the outbreak that can be used to resolve uncertainty in this parameter. We show how this interacts with estimates of vaccine efficacy and use it to formulate state- and time-dependent estimated thresholds for the implementation of a mass vaccination campaign. We extend this to cover uncertainty in multiple epidemiological parameters in a mechanistic way.

5.4.1 Effect of unknown transmission rate

We incorporate uncertainty in the transmission rate β using a $Gamma(k, \theta)$ prior, as described in the previous chapter (Section 4.2.4). If we do not gather real-time information relating to β, as we are with vaccine efficacy through the vaccine trial, the distribution of β remains unchanged throughout, regardless of the result of the vaccine trial. As such, the variance of the prior distribution has a significant effect on out recommendations regarding thresholds and vaccine trial timing (Figure 5.14).

If the variance is large, we find that it is best to act as early as possible. This may seem unintuitive, since it does not allow us time to reduce uncertainty in vaccine efficacy. However, it results from the fact that, at higher values of β, the delay until a campaign is started has significantly more effect on the outcome of the campaign (Figure 5.15). For example, if $\beta = 0.9$ ($R_0 = 4.5$), a delay of over 70 days will render a vaccination campaign ineffective, regardless of the vaccine efficacy. In contrast, for low values of β or R_0, the delay has little effect on the outcome of a vaccination campaign. Therefore, as the variance increases and both low and high values of β become more probable, the sensitivity to the delay at high values of β begins to dominate, causing the benefits of a quickly implemented campaign to outweigh the benefits of learning. Note, however, that we are also less likely to implement a campaign at all, given the higher efficacy required to ensure a low probability of increasing deaths through vaccination. As a result, the expected number of deaths remains close to what we would expect from not vaccinating at all and far from what we could achieve with perfect information, regardless of trial length or the value of ϵ.

As the variance of the prior on β decreases (Figure 5.14), the resolution of uncertainty in vaccine efficacy becomes more important, hence a longer trial would be recommended. For very low variances, we require less time to resolve uncertainty, hence the optimal trial length decreases again, approaching what we observed with a fixed β. The lower the variance in β, the more likely we are to vaccinate overall and the closer we come to achieving what we could with perfect information.

Overall, the incorporation and definition of uncertainty in the transmission rate

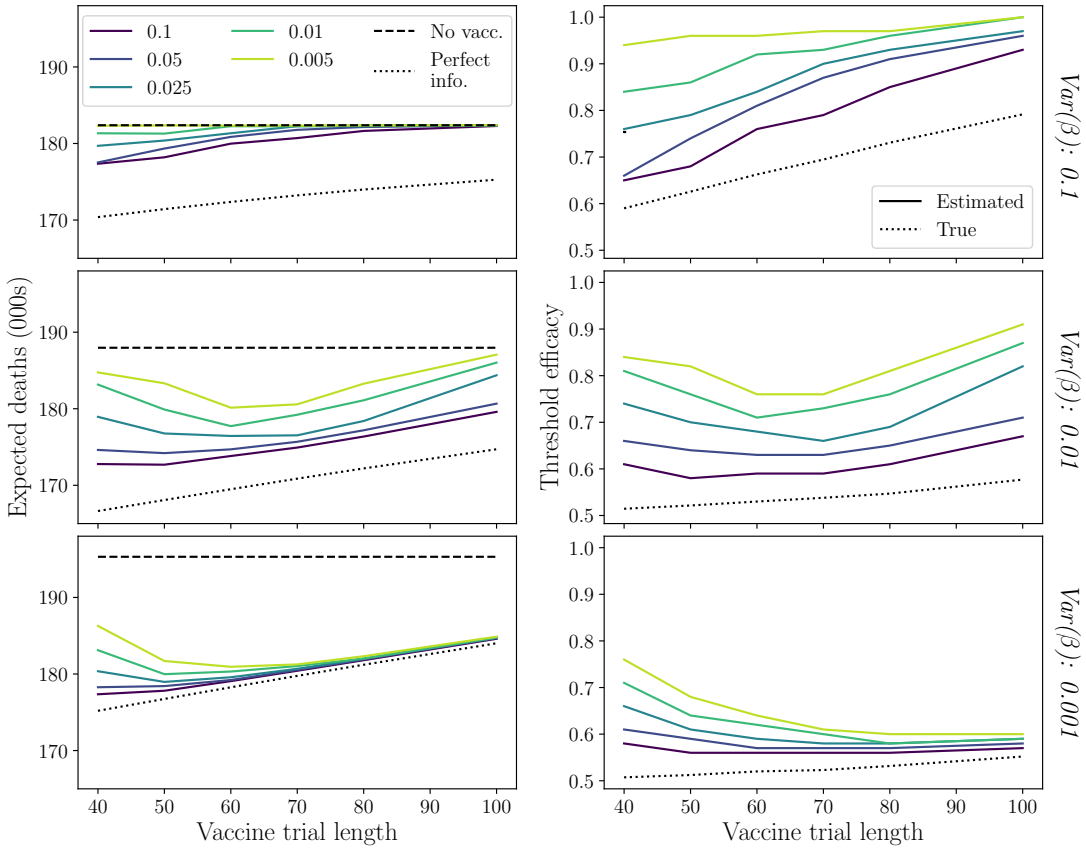


Figure 5.14: **Effect of unknown transmission rate on outcome and thresholds.** We calculate the expected number of deaths (left) and true and estimated vaccine efficacy thresholds (right; dotted and solid respectively) for a range of vaccine trial lengths (x-axis) and values of ϵ (colours), using different prior distributions of β (rows). The priors are contrasted by their variance (decreasing down rows), and are all centred at 0.4. In the left-hand plots, the dotted line shows the expected number of deaths achievable with perfect information. Other parameters are set to their default values, given in Table 5.1.

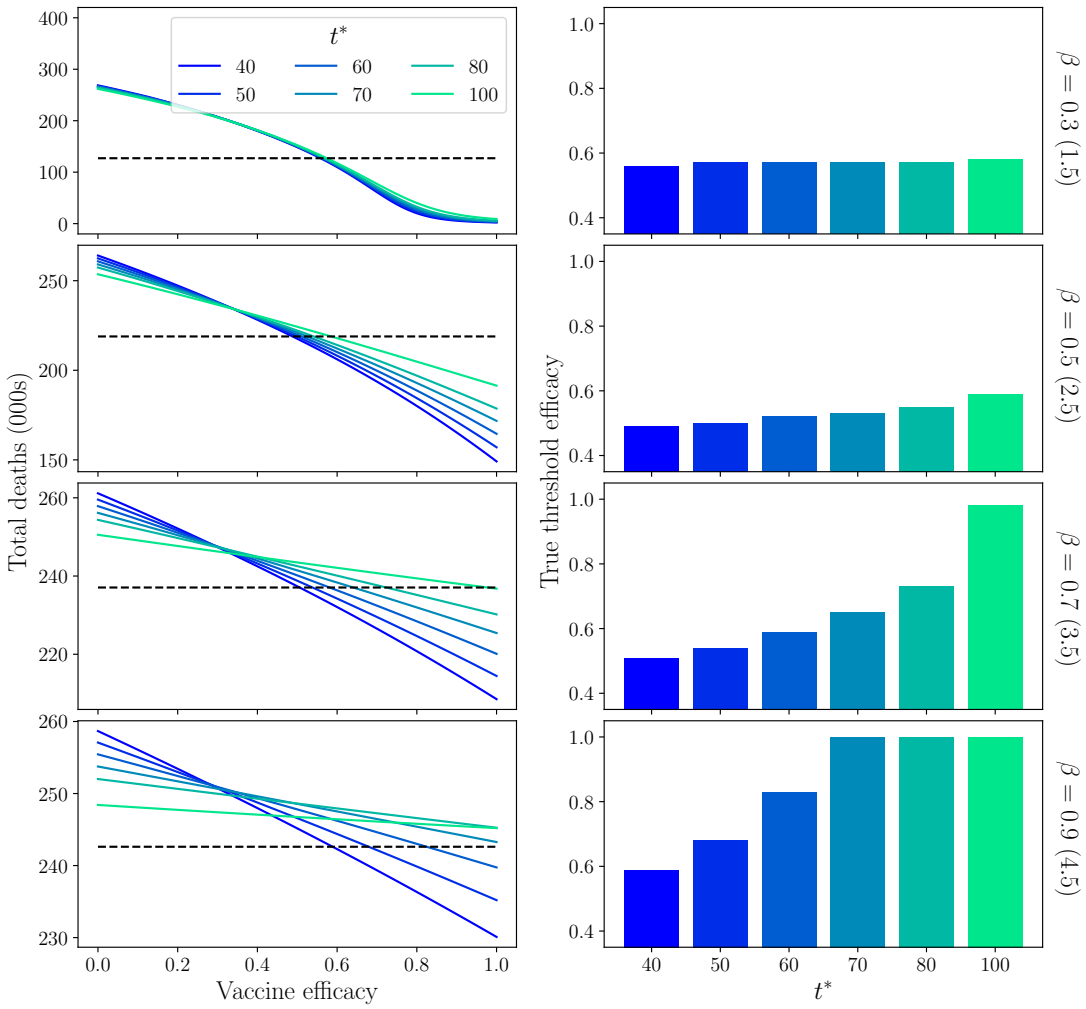


Figure 5.15: **Outcome of mass vaccination campaign for different values of transmission rate.** Left: total number of deaths from the outbreak, under a mass vaccination campaign implemented after a range of delays (t^*; colours), for a range of values of vaccine efficacy (x-axis) and β (rows). Corresponding values of R_0, calculated via Equation 5.3, are given in brackets. The dashed black line shows the total number of deaths in the absence of vaccination. Right: the true value of efficacy required to decrease the number of deaths through mass vaccination, for a range of delays (x-axis) and values of β (rows). Other parameters are set to their default values, given in Table 5.1.

significantly alters if and when we should implement a vaccination campaign. If the level of uncertainty is very high, it can render the resolution of uncertainty in vaccine efficacy redundant, or have the opposite effect and require us to spend more time resolving uncertainty in vaccine efficacy before making a decision whether or not to vaccinate.

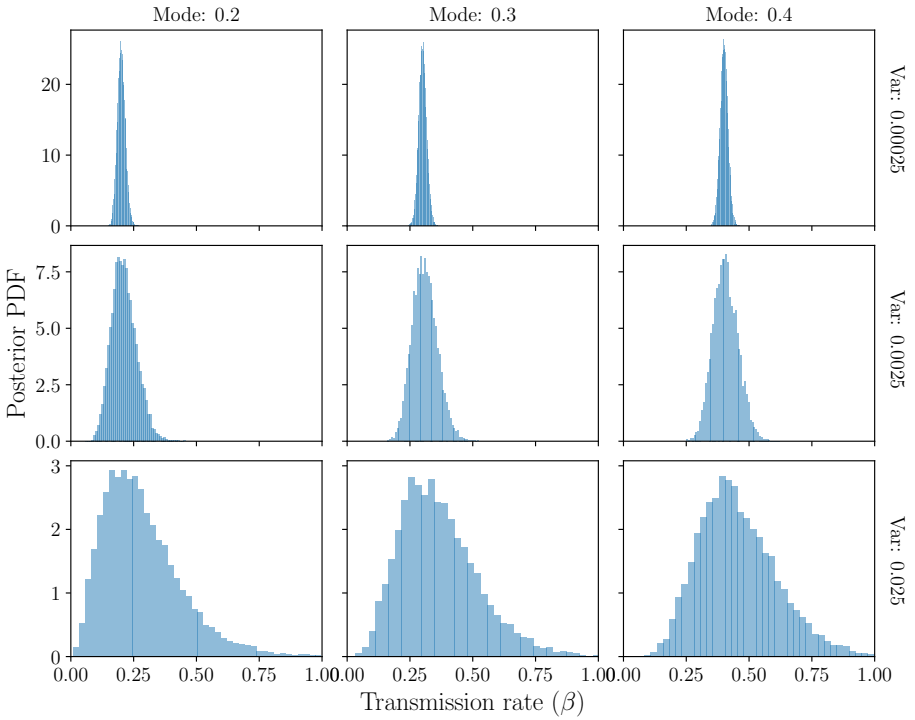


Figure 5.16: **Posterior distributions of transmission rate.** We display the *Gamma* posterior for β, for a range of modes (columns) and variances (rows).

5.4.2 Abstract measurement of transmission rate

Given the significant effect that an unknown transmission rate has on our control and monitoring recommendations, it would be beneficial to resolve uncertainty in this parameter at the same time as resolving uncertainty in vaccine efficacy. We first assume that we are able to measure the transmission rate and obtain a well-defined posterior distribution. We assume that the measurement of β results in a $Gamma(k, \theta)$ posterior distribution with an observable mode and variance. The mode and variance can be varied to represent different levels of uncertainty for different true values of β (Figure 5.16).

We assume that the measurement of β, and the resulting posterior, is obtained at the same time that a measurement of ν_e is obtained from a vaccine trial (t^* days after disease detection). Note that it is important to incorporate the posterior distribution of β when calculating the posterior distribution of ν_e. As shown in Figure 5.9, a higher value of β generally leads to a less variable distribution of estimates. Hence, as the location of our distribution around β increases, we find the posterior distribution around vaccine efficacy, obtained from the same estimate, will become more precise (Figure 5.17). However, since vaccination has not taken place in the population from

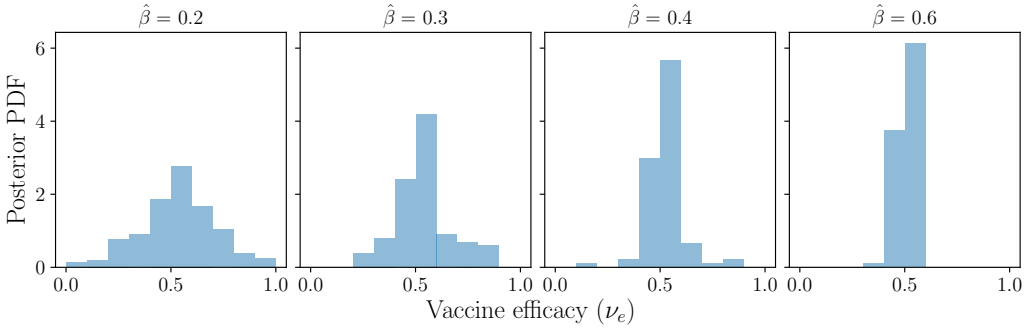


Figure 5.17: **Posterior distributions of vaccine efficacy.** We display the empirical posterior distributions for ν_e, obtained via Equation 5.5, dependent on the posterior mode of β (columns).

which we measure the transmission rate, this effect only occurs in one direction: our estimate of vaccine efficacy does not change the resulting posterior distribution around β.

By varying the mode and variance of the β posterior distribution and calculating the posterior distribution obtained for vaccine efficacy from a range of estimates, we are able to identify the estimated threshold required to implement a vaccination campaign conditioned on the observed transmission rate. We do so for estimates taken at a range of time points during the outbreak (Figure 5.18). As expected, the posterior distribution we obtain for β has a significant impact on the recommended thresholds for implementing a mass vaccination campaign. If the posterior has a low variance, the true and estimated thresholds will be closer, hence the estimated threshold is generally lower than for posteriors with high variance. If the mode of the posterior is below 0.3, we require a higher estimate of vaccine efficacy than if it is between 0.3 and 0.6, due to the interaction between posteriors seen in Figure 5.17. Over time, the thresholds can change significantly, generally increasing as time passes, due to the longer delay before implementing a campaign. The estimated threshold values for higher modes are more sensitive, since the outbreak progresses more quickly for such values, exacerbating the decreased effectiveness of a delayed campaign. The thresholds are most stable over this timeframe for β posteriors with modes close to 0.4 and with low variance.

5.4.3 Mechanistic measurement of transmission rate

Whilst we have provided a state- and time-dependent recommendation for the implementation of a mass vaccination campaign in Figure 5.18, our reliance on an

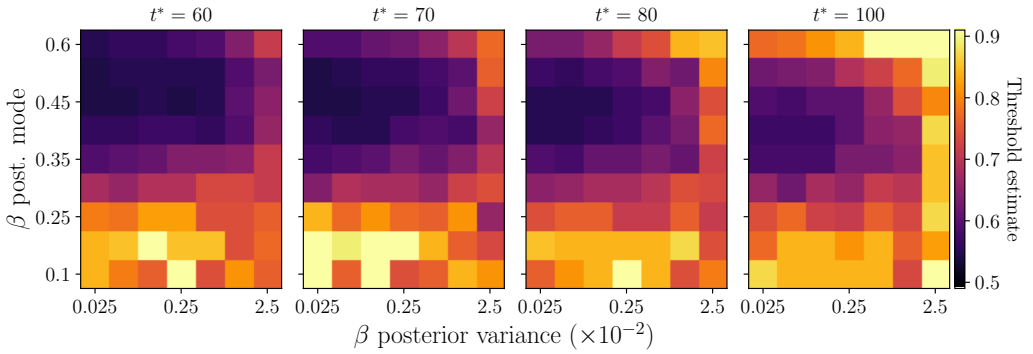


Figure 5.18: **Multidimensional, time-dependent estimated efficacy thresholds, using abstract measurement of transmission rate.** We calculate the estimated efficacy threshold required for $\epsilon = 0.05$, for a range of modes (y-axis) and variances (x-axis) of the β posterior distribution, for estimates taken at different points in time during a vaccine trial (columns). We assume an abstract measurement of β, which provides a *Gamma* posterior with observable mode and variance. Other parameters are set to their default values, given in Table 5.1.

abstract definition of the measurement of β has its restrictions. For example, if it is necessary to have a vaccine trial with a predetermined length, thus allowing us only a single decision point, we are unable to use this definition to recommend an optimal trial length, since it does not include a mechanism of how uncertainty in β may change over time. Furthermore, we are unable to give an indication of the expected outcome of the epidemic, since we are not able to specify the probability of a posterior with a specified mode and variance occurring. In this final section, we develop a mechanistic measurement of β to address these limitations.

We define and resolve uncertainty in β using a Bayesian fitting procedure. We use an uninformative prior distribution for β, given by a *Gamma* distribution with mode 0.4 and variance 0.1. Whilst we focus on the resolution of uncertainty in the transmission rate β, to increase the level of uncertainty we also assume that the incubation σ and recovery γ rates are unknown, although with informative priors based on our knowledge of these parameters (*Beta* distributions with modes $\frac{1}{9.4}$ and $\frac{1}{7.4}$ respectively and variance 5×10^{-4}). Real-time information is collected in the form of daily reported cases, assuming that all individuals who seek healthcare will be reported as infectious, without delay. We use a *Negative Binomial* distribution to define the likelihood of reported cases, parameterised by the mean rate (given by the movement from E and V_E to I_H in Equation 5.1) and an unknown overdispersion parameter. We use the latter to incorporate a higher level of variability in the simulated data. Details of the priors, real-time data, likelihood function and fitting procedure are given in Box 5.

Box 5: Mechanistic measurement of β

In this box we outline a mechanistic method of estimating unknown epidemiological parameters (transmission β, incubation σ and recovery γ) from real-time information collected throughout the outbreak.

Data

The real-time information is made up of daily reported cases $Rep(t)$, $t_0 \leq t \leq t^*$. We assume that all infectious individuals who seek healthcare are reported at the time of symptom onset.

Likelihood

The daily number of reported cases, $Rep(t)$, depends on the number of individuals currently exposed to the disease, both unvaccinated $E(t)$ and vaccinated $V_E(t)$, the incubation rate σ and the healthcare-seeking probabilities h and h_v.

We use a Negative Binomial distribution, with unknown overdispersion parameter ϕ, to define the likelihood:

$$Rep(t) \mid \theta \sim NegBinom\left(\sigma(hE(t) + h_v V_E(t)), \phi\right), \tag{5.6}$$

where $\theta = \{\beta, \sigma, \gamma, \phi\}$ are the unknown parameters to be fitted.

Prior distributions

We use an uninformative prior distribution for β, based on a *Gamma* distribution with mode 0.4 and variance 0.1.

We use informative priors for σ and γ, represented by *Beta* distributions with modes $\frac{1}{9.4}$ and $\frac{1}{7.4}$ respectively and variance 5×10^{-4}.

We use an uninformative prior for the overdispersion parameter ϕ, given by a $Gamma(3, 4)$ distribution (hyperparameters: shape, rate).

Posterior

We implement a Hamiltonian Monte Carlo (HMC) fitting procedure using the Stan programming language (Section 2.3.2), interfacing with Python via PyStan, to obtain posterior distributions of β, σ, γ and ϕ.

We simulate the process of gathering real-time information and calculating posteriors for the unknown epidemiological parameters over a range of true β values and time frames (Figure 5.19). Each simulation of the resolution in epidemiological parameter uncertainty is combined with a range of estimates of vaccine efficacy, $\hat{\nu_e}$, giving a joint posterior for both epidemiological and control parameters. Given the

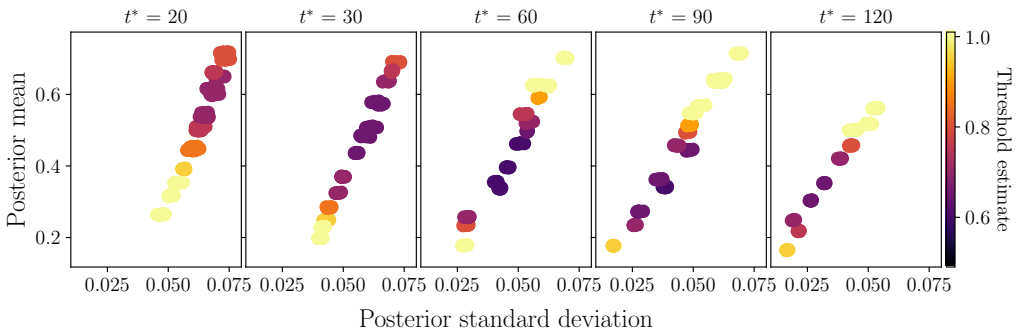


Figure 5.19: **Multidimensional, time-dependent estimated efficacy thresholds, using mechanistic measurement of transmission rate.** We calculate the estimated efficacy threshold required for $\epsilon = 0.05$, using multiple simulations of the mechanistic model for measuring β outlined in Box 4, for estimates taken at different points in time during a vaccine trial (columns). True values for β, σ and γ are drawn from their respective prior distributions within each simulation. Other parameters are set to their default values, given in Table 5.1.

effect that β measurements have on the posterior of ν_e, observed in Figure 5.17, it is essential that the posteriors are calculated conditionally. The posteriors are then used to simulate forward the epidemic with and without the implementation of a mass vaccination campaign, giving a distribution of total deaths for each. As before, we identify the minimum estimate of efficacy that results in a probability of increasing the number of deaths through vaccination of less than 5% (Figure 5.19).

We find that the variance of the posterior for β is strongly related to both the mean of the posterior and the length of the monitoring period (Figure 5.19). In general, posteriors with a larger mean will also have a larger variance, however this decreases the longer we spend on monitoring, with posteriors located at lower values of β responding the most to lengthened monitoring periods (Figure 5.20). The estimate of efficacy required to implement a mass vaccination campaign behaves similarly to what we observed under an abstract measurement of β (Figure 5.18): at higher values of β, we are more likely to implement a campaign after a short monitoring period compared to long, however this is the opposite at low values of β. In Figure 5.20, 3rd panel, we see that, for high values of β, the estimated threshold starts low but quickly increases towards 1. This is due to the epidemic taking off very quickly, allowing for faster resolution of β but requiring a highly effective vaccine to have a worthwhile impact. However, at lower values of β, the slower epidemic results in slower resolution of uncertainty, but we also have more time to resolve uncertainty. Overall, we find the optimal length of the monitoring period to be 30 days, in order to minimise the expected number of deaths (Figure 5.21). Stopping the monitoring

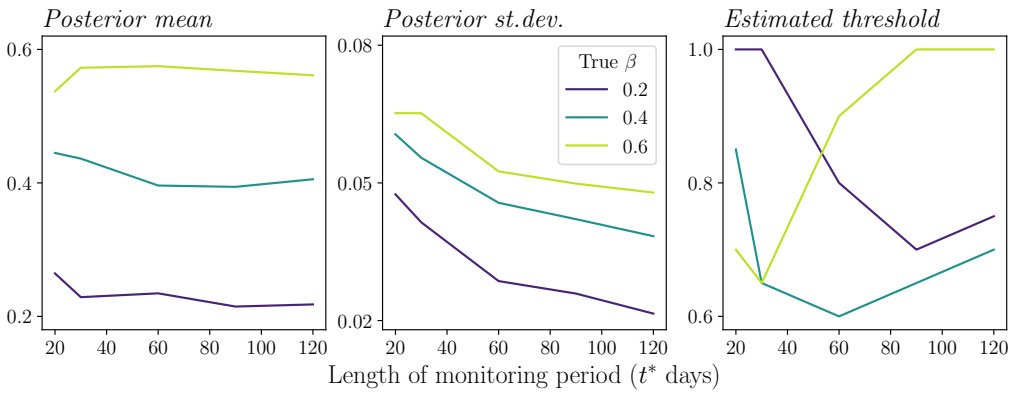


Figure 5.20: **Effect of length of monitoring period on transmission rate posteriors and estimated thresholds.** We select three specific simulations from those performed in Figure 5.19, defined by true values of $\beta = 0.2, 0.4, 0.6$, and record the posterior mean (left), posterior standard deviation (centre) and estimated vaccine efficacy threshold (right) for a range of lengths of the monitoring period. Other parameters are set to their default values, given in Table 5.1.

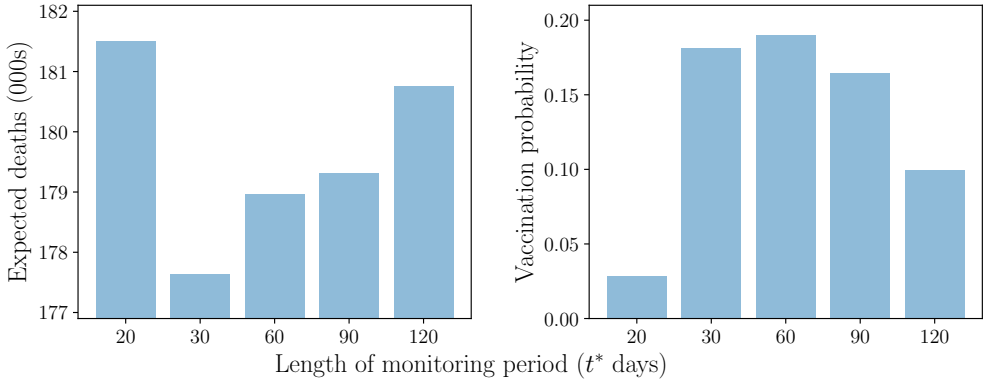


Figure 5.21: **Effect of length of monitoring period on outcome and probability of vaccination.** Left: we calculate the expected number of deaths, using the state-dependent thresholds identified in Figure 5.19, for a range of lengths of the monitoring period. Right: we calculate the probability that a mass vaccination campaign is implemented, using the state-dependent thresholds identified in Figure 5.19, for a range of lengths of the monitoring period. Other parameters are set to their default values, given in Table 5.1.

before this results in a very low probability of implementing a vaccination campaign, given the high level of uncertainty remaining in the parameters. The probability of vaccinating increases for lengths up to approximately 60 days, however this does not reduce the overall expected cost due to the increased delay to implementation. For monitoring periods longer than 60 days, the delay necessitates an increasingly high vaccine efficacy, resulting in a decreasing probability of implementing a campaign.

5.5 Conclusions and discussion

In this chapter, we have used AM in a more realistic, human-disease scenario to both exhibit the type of useful information than AM can provide in complex situations and how different uncertainties can interact with each other. We introduced a disease model based on a model in the literature describing Ebola [144], observing that the establishment of healthcare centres to treat and isolate infectious individuals can dramatically reduce the number of deaths from an outbreak. However, with the incorporation of a mass vaccination campaign, we found that an increase in risky behaviour from vaccinated individuals, incoporated as a reduced probability of seeking healthcare, can give rise to an increase in the number of deaths if the efficacy of the vaccine is low. In light of such information, it is clearly beneficial to adopt an adaptive approach to the use of such a campaign, allowing implementation to be delayed until the uncertainty in vaccine efficacy is reduced. We can then formulate a monitoring plan to target this uncertainty, in this case using a vaccine trial. We used a stochastic model of the trial population to describe the resolution of uncertainty mechanistically, enabling us to predict the amount of uncertainty resolution over time and thus plan the possible implementation of a mass vaccination campaign in the future in response to the results from the trial.

We incorporated a different perspective on the management objective compared to previous chapters, requiring that the probability of increasing the number of deaths through mass vaccination be bounded by a specified value ϵ. Thus, we will only implement a mass vaccination campaign if we are reasonably sure that it will be effective in reducing the number of deaths. We showed that, using the components of the AM framework, including a stochastic vaccine trial model, we are able to formulate state- and time-dependent thresholds for the implementation of a mass vaccination campaign, that meet this requirement.

Whilst following these thresholds enables us to largely avoid any possible negative outcomes from a mass vaccination campaign, it can also result in a significant opportunity cost caused by foregoing vaccination when the true efficacy is high enough to reduce the number of deaths, but the estimated efficacy is lower than the identified threshold. This inaction can lead to thousands more deaths than necessary. However, we are able to use our framework to optimise the length of time spent monitoring before control is implemented, balancing the worth of uncertainty resolution and early action. Furthermore, to make the most of both increased knowledge where necessary and prompt action where possible, we are able to provide dynamic, time-dependent thresholds relying on multiple estimates taken over time

during the trial. Doing so results in fewer deaths compared to relying on only a single measurement, even when the timing is optimised, whilst keeping the probability of increasing deaths through mass vaccination constant.

The analysis of the opportunity cost also highlighted the significant effect of the parameter ϵ. This parameter represents how comfortable decision makers are with taking risks. If ϵ is high, greater risks are taken, which reduces the number of deaths on average, but increases the chance of an even larger outbreak. If ϵ is low, it is highly unlikely that we will cause a larger outbreak, however we are also less likely to see the rewards from a successful campaign. Using AM in this way, we can clearly show the effect of increasing or decreasing ϵ to decision makers, aiding them in setting it at an appropriate value.

If the epidemiological parameters, such as transmission, are also uncertain, this can have a significant impact on recommendations, especially if the uncertainty in epidemiological parameters can not be resolved through monitoring. If this uncertainty is very large, it can render learning about vaccine efficacy almost irrelevant. In such a case, it is recommended to perform only a very short vaccine trial, followed by either quick implementation of mass vaccination or none at all. If the uncertainty in epidemiological parameters is significant, but resolving uncertainty in vaccine efficacy is still relatively important, then longer vaccine trials would be recommended compared to when epidemiological parameters were known. This is due to the greater variation in vaccine trial estimates that arises from uncertain epidemiological parameters, requiring longer to resolve uncertainty. As the uncertainty decreases, so does the recommended length of trial. Thus, additional uncertainties in the system can significantly change the recommended timing and implementation of control and monitoring, even if they can not be resolved themselves.

We can incorporate a measurement of β to provide multidimensional state- and time- dependent thresholds. Doing so in an abstract way, by assuming the posterior of β will follow approximately a *Gamma* distribution with observable mode and variance, allows for convenient calculation of estimated efficacy thresholds conditioned on the observed posterior and time of estimate. We were also able to observe how measurements of β could affect our posterior belief regarding vaccine efficacy, even if the estimate of efficacy from a vaccine trial remained the same. This highlights the need to consider both measurements together and account for this interaction. However, this abstract method does not explicitly model the relationship between the posterior variance, posterior mean and time, thus does not allow us to optimise timing or provide an accurate indication of the expected number of deaths from the outbreak. These limitations were explored in detail in the previous chapter.

Instead, we must define the measurement of β, and resulting posterior distribution, in a mechanistic way.

Using daily reported cases from the healthcare centres within a Bayesian framework, we were able to predict the resolution of uncertainty in β over time. We identified a strong relationship between the posterior variance and posterior mean, with higher means generally leading to higher variance, and posteriors with lower means becoming more precise faster. Using this, we were able to identify an optimal monitoring length of approximately 30 days.

This chapter has seen the use of AM in a different context to previous chapters, focusing on providing useful information to decision makers in a more complex setting. However, there remain limitations in the scenario and models we have used. For example, we have again used a deterministic model to describe the system. In reality, the dynamics would exhibit significant stochasticity. This is especially true for the transmission rate β, which, for Ebola, has been shown to exhibit significant variation throughout an outbreak [32, 36]. This would reduce our ability to resolve uncertainty in this parameter over time and significantly alter how we perform forecasts and thus assess the use of controls in the future. However, this also highlights the need for specific, mechanistic models of uncertainty resolution that can be used within the AM framework.

The stochasticity in epidemiological parameters would also affect the estimates from the vaccine trial model. Although we simulated the vaccine trial stochastically via the Gillespie algorithm, the parameters themselves were assumed fixed throughout. Hence, the amount of variation in the estimates would be significantly greater in real life. This would result in requiring significantly larger and longer trials to resolve uncertainty than we have suggested in this chapter. The context of the trial itself was not completely realistic, as we assumed an identical, isolated population. In reality, the trial itself can have a significant effect on the disease dynamics within the population [145, 151]. We believe active AM could be extremely beneficial in such a scenario also, where the experimentation of an unknown control and the benefit of uncertainty resolution must be weighed against the possible negative outcomes of that control.

The relevance of the set-up used in this chapter is also not explicitly supported in the literature. For example, it is not clear whether individuals would be less likely to seek healthcare if vaccinated. Furthermore, such an effect may depreciate over time as people lose faith in a vaccine that is clearly not effective. There are also non-trivial considerations surrounding the ethics of the management procedure

implemented. For example, we have assumed that there is little prior knowledge regarding the vaccine efficacy (a wide prior distribution on ν_e), however, it may be that a trial could only be undertaken if there was significant evidence that the vaccine is highly effective. This could greatly reduce the utility of an active AM procedure in a real-world context.

Finally, we fixed various parameters within the model that could have a significant effect. As shown in this chapter, the inclusion of uncertainty within these parameters can have a significant effect on the recommendations regarding control and monitoring. However, a high number of uncertainties makes it difficult to clearly portray state-dependent recommendations, a difficulty recognised in the literature [14], thus are often investigated independently. In the next chapter, we address the effect of the healthcare-seeking behaviour of the population, which was fixed in this chapter, in a new scenario. We also discuss how the results from these two chapters could interact with each other.

Although there are limitations to this work, we believe it makes a valuable contribution to the literature. We have shown that active AM can be used to identify thresholds for triggering the implementation of a mass vaccination campaign, that are both dynamic and state-dependent. Such triggers are highly relevant and often analysed outside of AM [25, 28, 29, 152]. Furthermore, the identification of interacting uncertainties and measurements has implications for the appropriate application of AM in real-world scenarios, motivating active AM and mechanistic models of uncertainty resolution that can incorporate such effects.

Chapter 6

Managing healthcare-seeking behaviour to avoid overloading the healthcare system

Abstract

We use our Ebola-like disease model to analyse the effect of overloading the healthcare system. We demonstrate that an increased probability of seeking healthcare can greatly reduce the severity of the outbreak, by isolating infectious individuals from the community and stopping further spread. However, this may put pressure on the healthcare system due to greater numbers of patients, which can lead to increased loss of life if the system is not equipped to deal with this pressure. We introduce a decision making problem surrounding the targeting of the healthcare-seeking behaviour of the population: different levels of intervention can be used to raise the healthcare-seeking probability of symptomatic individuals. We use a multi-phase AM procedure to guide the use of such interventions, greatly improving the outcome of the epidemic compared to both no intervention or static intervention. Finally, we show how anticipating uncertainty resolution under an active AM approach to this problem can change initial recommendations, greatly reduce the size of the epidemic and provide vital information to decision makers regarding the value of resolving uncertainty in specific parameters.

6.1 Introduction

In this final chapter we analyse the effect that the healthcare-seeking behaviour of the population can have on the outcome of an epidemic and recommendations for control. We use the same Ebola-like disease model from the previous chapter (Section 5.2.1), assuming the establishment of healthcare centres that aim to isolate and treat infectious individuals. We make a simple addition to this model, allowing a small proportion of non-infected individuals to also be admitted into healthcare. This is based on the assumption that during an outbreak, there may be people who present with similar symptoms as the disease in question, but who do not actually have the disease. This is applicable for a disease such as Ebola, which presents with symptoms similar to malaria or other commonly circulating, less infectious, diseases during the early stages of infection.

We use this model to analyse how a different healthcare-seeking probability, h, can affect the overall burden on the healthcare system. We incorporate the idea of a capacity on the healthcare system and a penalty for exceeding this capacity. Whilst an increase in the healthcare-seeking probability can significantly improve the outcome of the epidemic, we find that it can also increase the burden on the healthcare system. This is especially true in the presence of a high proportion of non-infected healthcare-seekers. As a result, if an increase in the healthcare-seeking probability causes the burden on the healthcare system to exceed capacity, this can have undesirable effects on the outcome of the epidemic, resulting in a higher number of deaths.

We incorporate the use of the AM framework into a management scenario in which we target the healthcare-seeking rate h to control the outbreak. We assume that, through interventions such as community engagement, it is possible to increase the probability that someone will seek healthcare when symptoms appear. We allow three levels of targeted intervention: none, low and high. We assume that these interventions cause a gradual increase in the healthcare-seeking probability, with high level targeting resulting in a steeper gradient, and without intervention the behaviour of the population does not change. We allow the intervention to be changed at multiple points throughout the outbreak, resulting in a multi-phase decision process. We assume that there are several sources of uncertainty: in the normal, pre-intervention healthcare-seeking behaviour of the population, the proportion of healthy individuals who present with similar symptoms from a different disease and the effect that interventions have on the healthcare-seeking behaviour.

We approach the decision making process from both a passive standpoint, using

only prior information to make our initial decisions, and an active standpoint, aniticipating the resolution of uncertainty in the future. This provides another example of a scenario in which passive and active AM lead to different decisions. Within the active AM approach, we use the EVFPI measure introduced in Chapter 4 (Section 4.3.1; Equation 4.9) to quantify the value of resolving uncertainty in the future. Thus, we assume that we will obtain perfect information regarding the unknown parameters. We also use this measure to clearly portray the cost of delaying uncertainty resolution, or the benefit of prioritizing it, and how decisions made early on in the outbreak can effect this. Finally, we analyse the importance of different sources of uncertainty using the EVPXI measure (Section 2.2; Equation 2.4) and the benefit of experimentation of interventions with unknown effect.

Overall, we show that targeting the healthcare-seeking behaviour of the population through community-based interventions can significantly reduce the expected number of deaths from an outbreak. However, the use of an active AM approach can improve outcomes further, maximising benefit and reducing the probability of overloading the healthcare system. Furthermore, anticipating the resolution of uncertainty in the future can alter the recommended course of action at the start of the outbreak, as well as provide clear information regarding the benefit of uncertainty resolution and the cost of delaying such resolution.

6.2 Burden on the healthcare system

First, we make some simple additions to the Ebola-like disease model introduced in the previous chapter and define the 'burden' on the healthcare system.

6.2.1 Healthcare-seeking probability and peak burden

We have already seen that increasing the healthcare-seeking probability within the current Ebola-like disease model will decrease the total number of deaths, through a decreased R_0 (Figure 5.3). However, the healthcare system may be shouldering a larger burden because of it. We define the burden on the healthcare system to be the maximum number of people within healthcare at any one time. We find that the relationship between h and the burden on the healthcare system is less obvious than that with the total number of deaths (Figure 6.1). For low h, a small increase will lead to a higher peak number of infectious individuals seeking healthcare. However, for larger values of h, further increases will result in a lower peak. This is due to a greatly reduced R_0 during the early stages of the outbreak, which result in

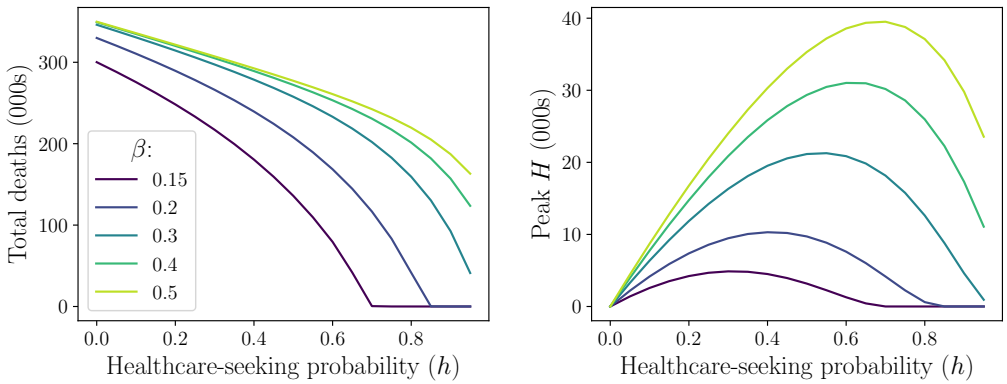


Figure 6.1: **Effect of the healthcare-seeking probability.** We vary the healthcare-seeking probability h and record the total number of deaths (left) and maximum number of people within healthcare (right) for a range of transmission rates (colours). The value of h is assumed to take effect on the day that the outbreak is detected and remains constant throughout the outbreak. Other parameters are set to their default values given in Table 5.1 in the previous chapter.

significantly fewer infections overall.

6.2.2 Existence of non-infected healthcare-seekers

In the previous chapter we assumed that all individuals who seek healthcare will be infectious. However, this may not be the case. For many diseases, including Ebola, early symptoms can resemble those of much more common, less serious diseases or health issues, such as a common cold or flu. Hence, during an outbreak, there may be a significant number of 'healthy' (not infected with the disease in question) individuals seeking healthcare. This can add to the burden on the healthcare system. We include this in the model by assuming that a fixed proportion h_s of healthy, susceptible individuals (S) will have a minor health issue that presents will similar symptoms. These individuals are equally likely to seek healthcare as infected individuals (i.e. seek healthcare with probability h), however will only remain in healthcare for a single day before being discharged back into the community. We assume that such individuals will not be infected during this period.

The existence of healthy healthcare-seekers will increase the burden on the healthcare system and can significantly alter the relationship between h and the peak burden (Figure 6.2). If h_s is large enough, the increased number of healthy healthcare seekers for large h can outweigh the reduced number of infected healthcare-seekers, causing an overall increase in the peak burden on the system.

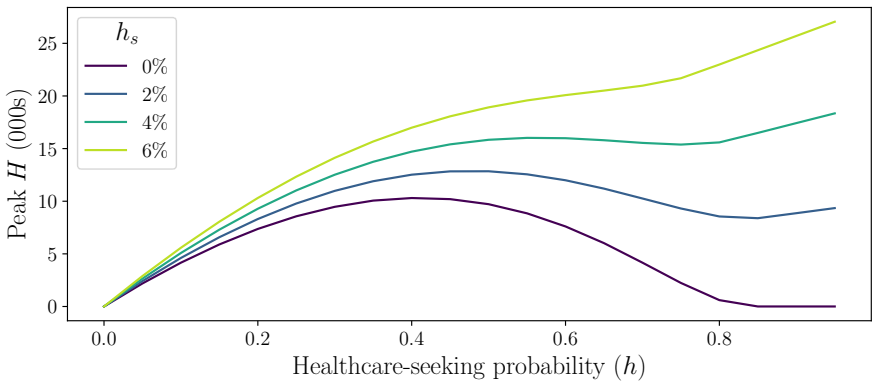


Figure 6.2: **Effect of healthy healthcare-seekers.** We show the relationship between h and the maximum number of people within healthcare (y-axis) for different levels of healthy healthcare-seeking behaviour (h_s; colours). The parameter h_s represents the proportion of people in the population who have similar symptoms, but are not infected with the disease in question. The values of h and h_s are assumed to take effect on the day that the outbreak is detected and remain constant throughout the outbreak. We let $\beta = 0.3$. Other parameters are set to their default values given in Table 5.1 in the previous chapter.

6.2.3 Exceeding the capacity of the healthcare system

An increased burden on the healthcare system can become an issue if there are limited resources which may be exceeded, such as space, equipment and medicines. We introduce a penalty for exceeding the capacity of the healthcare system, incurred if the number of individuals currently in healthcare exceeds a given limit (H_{cap}). We implement this penalty by not allowing any further admissions for a fixed period of time (τ). By doing so, the effect that h has on the peak number of healthcare-seekers can now also have a significant effect on the total number of deaths (Figure 6.3). Where before a higher healthcare-seeking probability always lead to a reduced number of deaths (Figure 6.1), we now find that keeping the number of healthcare-seekers just below the maximum capacity is more optimal. Once capacity is reached, this can cause a sharp resurgence in the number of deaths.

6.3 Healthcare-seeking probability as control

Given the significant effect that the healthcare-seeking behaviour of the population has on the outcome of the epidemic, it makes sense to try to exploit it as a form of control. Throughout the remainder of this chapter, we assume that the healthcare-seeking probability h can be increased through some form of community engagement.

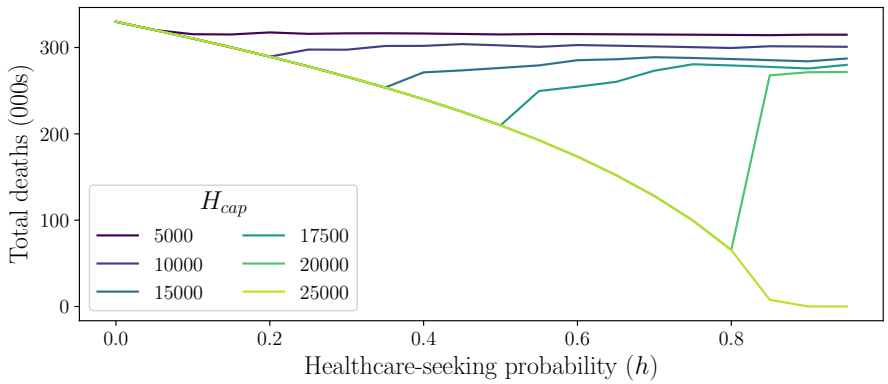


Figure 6.3: **Effect of healthcare system capacity.** We show the relationship between h and the total number of deaths resulting from the outbreak (y-axis) for different limits on the capacity of the healthcare sytem (H_{cap}; $colours$). The parameter H_{cap} represents the maximum number of people that can be within healthcare at any time. If this is exceeded, the healthcare system is overloaded and will not accept new patients for a period of 14 days ($\tau = 14$). The values of h and H_{cap} are assumed to take effect on the day that the outbreak is detected and remain constant throughout the outbreak. Other parameters are set to their default values given in Table 5.1 in the previous chapter.

We assume that the probability without intervention is h_0 and increases towards 1 during intervention. This is defined assuming that the difference between the current probability and 1 decreases by a constant proportion Δ_h:

$$\frac{dh(t)}{dt} = (1 - h(t))\Delta_h.$$

Letting x be the time since the intervention began and assuming $h(0) = h_0$, we can solve this to obtain

$$h(x) = (h_0 - 1)e^{-\Delta_h x} + 1. \tag{6.1}$$

This results in a variable h, which responds quickly to intervention at first but slows down as it approaches 1 (Figure 6.4). We assume that h_0 is fixed, but unknown, and we are able to control the rate of change Δ_h through the intensity of our intervention.

The outcome of such an intervention is heavily dependent on both the initial probability of seeking healthcare, h_0, and the proportion of the healthy population expected to present with similar symptoms, h_s (Figure 6.5). We find that the same intervention (same Δ_h) can result in as low as 50,000 deaths, or as high as 300,000 deaths, for very small changes in either h_0 or h_s. For the remainder of this chapter, we analyse how adaptive management can be used to inform interventions targeting h under these uncertainties.

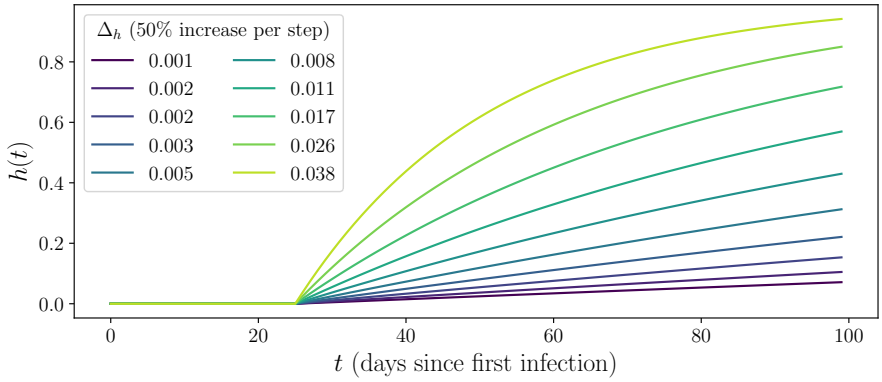


Figure 6.4: **Effect of intervention targeting healthcare-seeking behaviour.** We calculate the value of the healthcare-seeking probability h over time, assuming it follows Equation 6.1, for a range of Δ_h (colours), representing different levels of intervention (more intervention $\rightarrow$ greater Δ_h). We assume that the intervention causing h to increase starts as soon as the outbreak is detected and the healthcare-seeking probability without intervention (h_0) is 0.

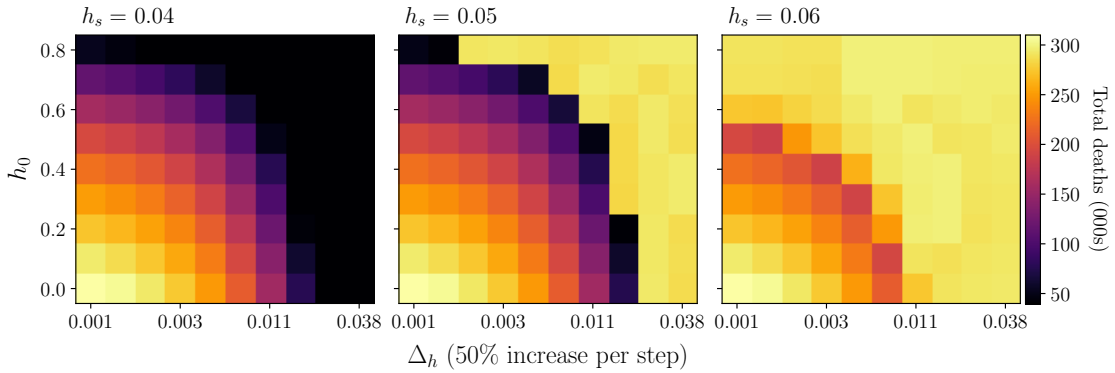


Figure 6.5: **Effect of increasing h on outcome of epidemic.** We vary the rate of increase in h (Δ_h; x-axis), the healthcare-seeking probability without intervention (h_0; y-axis) and the proportion of healthy healthcare-seekers within the population (h_s; left-to-right) and record the total number of deaths resulting from the outbreak (colour). We assume that the intervention causing h to increase starts as soon as the outbreak is detected and continues for 90 days. Other parameters are set to their default values given in Table 6.1.

Table 6.1: **Summary of parameters and notation used.** Default values apply throughout the chapter unless otherwise stated. Values left blank depend on the vaccination campaign and are calculated as required during the optimisation process. Values have been selected based on Figures 6.1 - 6.5 to reveal non-trivial dynamics: healthcare-seeking probability h can be increased without exceeding the capacity of the healthcare system, however if increased too much the system will be overloaded.

Notation	Description	Default value
h_s	Proportion of the healthy population with similar symptoms from a different disease, who may also seek healthcare	5%
H_{cap}	Maximum number of people the healthcare system can accommodate at one time, before becoming overloaded and not operating as it should	20,000
h_0	Healthcare-seeking probability of individuals without intervention	0.2
Δ_h	Rate of increase in h as a result of intervention, applied according to Equation 6.1	Low level: 0.01 High level: 0.03
τ	Length of time taken for healthcare system to recover from overloading	14 days
M	Number of decision points allowed during adaptive intervention process	5
$\{t_i\}$	Times of decision points during adaptive intervention process, represented as the number of days since outbreak detection	$\{0, 90, 180,$ $270, 360\}$

6.3.1 Adaptive interventions

We assume a multiphase intervention, with 5 decision points at times $\{t_i\} = \{0, 90, 180, 270, 360\}$. We consider three options for control at each decision point: 1) do not target the healthcare-seeking probability h, 2) low level targeting of h, and 3) high level targeting of h. The low and high level targeting result in different values for Δ_h (0.01 and 0.03 respectively), whilst no targeting results in a constant h ($\Delta_h = 0$). We also assume that a lower level of intervention targeted towards h will allow more resources to be utilised elsewhere, in this case to increase the maximum capacity of the healthcare system. We assume that the maximum capacity of the healthcare system is 20,000 (4% of the population). If there is no targeted intervention on h, we can increase the capacity by 2000 (10%), or by 1000 (5%) if there is only low level targeting of h. A summary of the control parameters and values used in this chapter are given in Table 6.1.

Assuming $h_0 \sim \mathit{Normal}(0.2, 0.05)$, $h_s \sim \mathit{Normal}(0.05, 0.01)$, and the control and default parameter values in Table 6.1, we are able to construct a decision tree of expected outcomes given different decisions (Figure 6.6). In this scenario, we find that the optimal intervention plan to minimise the expected number of deaths overall is high level targeting of h for the first 90 days, followed by no targeting for the rest of the outbreak, choosing instead to commit the extra resources to increasing the capacity of the healthcare system. This leads to more than a 40% decrease in the expected number of deaths compared to not targeting h at all. We could achieve a similar, though slightly worse, expected outcome from low level targeting of h in the first 90 days, followed by another period of low level targeting either between days 90-180 or 360-450. In general, we see that it is best to target h before the peak of the outbreak, helping to reduce the spread of the disease early and lower the peak number of infections and thus burden on the healthcare system. Whilst the outbreak is peaking, it is best to stop targeting h and reinvest the extra resources into increasing the capacity of the healthcare system. Finally, after the peak, it can be beneficial to again target h, however this depends on the amount it has been targeted already and the extent to which the disease has spread throughout the population. Later decisions also have much less of an effect overall than earlier decisions.

The timing and number of decision points plays a significant role in how well we are able to control the outbreak. In Figure 6.6, we have allowed 5 decision points, spaced at 90 day intervals throughout the outbreak. We now analyse the effect of having only a subset of these decision points (Figure 6.7). First, if we only have a

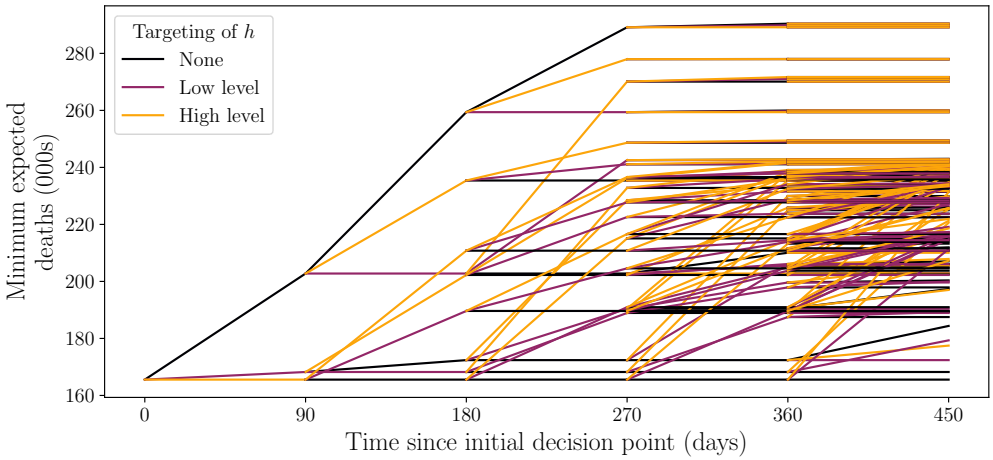


Figure 6.6: **Expected number of deaths for different multi-phase interventions.** We show all possible multi-phase interventions, assuming 5 decision points and a choice of high level targeting of h (yellow; $\Delta_h = 0.03$), low level targeting (maroon; $\Delta_h = 0.01$) or no targeting (black; $\Delta_h = 0$) at each decision point. Decision points are spaced at 90 day intervals, beginning on the day the outbreak is detected. At each branch of the tree, we record the minimum expected number of deaths, taken from all possible future paths that can be taken, conditioned on the decisions already made. Interventions chosen at the final decision point are assumed to continue for the remainder of the outbreak. We assume that h_0 and h_s are unknown, with priors $h_0 \sim \mathit{Normal}(0.2, 0.05)$ and $h_s \sim \mathit{Normal}(0.05, 0.01)$. All other parameters are assumed known with values given in Table 6.1.

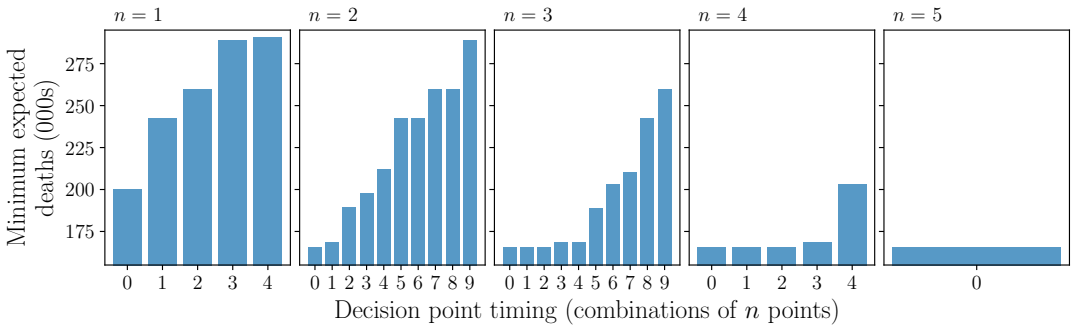


Figure 6.7: **Effect of timing and number of decision points on the outcome of interventions.** We vary the number of decision points (n; left-to-right) and the timing of decision points (x-axis) and record the minimum expected number of deaths achievable through interventions targeting h. We vary the timing of decision points in the same way as in Chapter 3, Figure 4.11: we allow 5 points at which decisions can be made, spaced at 90 day intervals throughout the outbreak, and take all possible combinations of n decision points. The first timing combination will have n decision points during the first n 90 day intervals. The last combination will have n decision points during the final n 90 day intervals. Interventions chosen at the final decision point are assumed to continue for the remainder of the outbreak. We assume that h_0 and h_s are unknown, with priors $h_0 \sim Normal(0.2, 0.05)$ and $h_s \sim Normal(0.05, 0.01)$. All other parameters are assumed known with values given in Table 6.1.

single decision point ($n = 1$), resulting in a static policy, the best outcome would be obtained from low level targeting of h throughout the outbreak. However, this results in an increase in the expected number of deaths of approximately 15% compared to the adaptive policy identified earlier. If we have at least one opportunity to adapt control ($n \geq 2$), we can obtain the same expected outcome as with 5 decision points, as long as the first two decisions are made on days 0 and 90. Decisions that are made later or are more spread out lead to a worse expected outcome.

6.3.2 EVFPI

Based on the analysis of Figure 6.6 in the previous section, the optimal recommendation appears to be an initial 90 period of high level targeting, followed by no targeting throughout the remainder of the outbreak. However, this represents a passive view of control, as it does not consider the possibility of resolving uncertainty before future decision points occur. We use the EVFPI measure, introduced in Chapter 4 (Section 4.3.1; Equation 4.9), to analyse how the possibility of resolving uncertainty in the future can change which decisions appear optimal at early stages of the outbreak.

We calculate the EVFPI, assuming that perfect information is achieved at different points throughout the outbreak (Figure 6.8). We also show the effect that different decisions made up to the point of uncertainty resolution have on the EVFPI. Following the optimal recommendation based on prior information alone (high level targeting for h for the first 90 days only), we see that the EVFPI falls to 0 after the first decision point. This suggests that, even in light of new information, there is no way of improving control in the future if we raise h to a very high level initially. Taking no action initially results in the EVFPI falling below 0 after the first decision point, showing that the lost opportunity to stem the spread of the outbreak early on outweighs the benefit from any future information and delayed control intervention.

The most important result is that low level targeting of h in the initial phase of control leads to a significantly slower depreciation of the EVFPI. By not raising h too much before gaining perfect information, we are able to avoid overloading the healthcare system by stopping targeting of h if h_s and h_0 prove to be higher than expected, or continuing targeting of h if the unknown parameters are equal or lower than expected. Hence, if we expect to gain accurate information regarding these parameters before the end of the outbreak, targeting h at a low level is the optimal initial decision, in contrast to our previous conclusion when ignoring future information.

Using the EVFPI measure, assuming that uncertainty is resolved at different points throughout the outbreak (Figure 6.8), we can clearly visualise the cost of delaying such resolution, or conversely, the benefit of prioritizing it. If uncertainty was resolved instantly, we could reduce the expected number of deaths by almost 100,000 people, a reduction of almost 60% compared to relying only on prior information. This is likely to be impossible, since it takes time to gather information and resolve uncertainty. Taking 90 days to do so reduces the benefit of resolving uncertainty by approximately 10,000 deaths (10%), but only if we implement low level targeting of h during this time. Implementing other intervention strategies will cause the value of new information to be lost completely. Taking an extra 90 days, thus resolving uncertainty 180 days from now, would result in a further loss of EVFPI of 20,000 deaths, on top of the previous loss. This requires stopping the targeting the h for this period. A delay of another 90 days would be even more serious, resulting in a further loss of of EVFPI of 40,000 deaths. Overall, delaying uncertainty resolution by 270 days would reduce the value of this information by 70%. If we expect this resolution to require longer than 270 days, this again changes the recommended interventions during this time. Instead of only a single period of low level intervention, we would recommend two consecutive periods of low level targeting. Hence, whilst there may

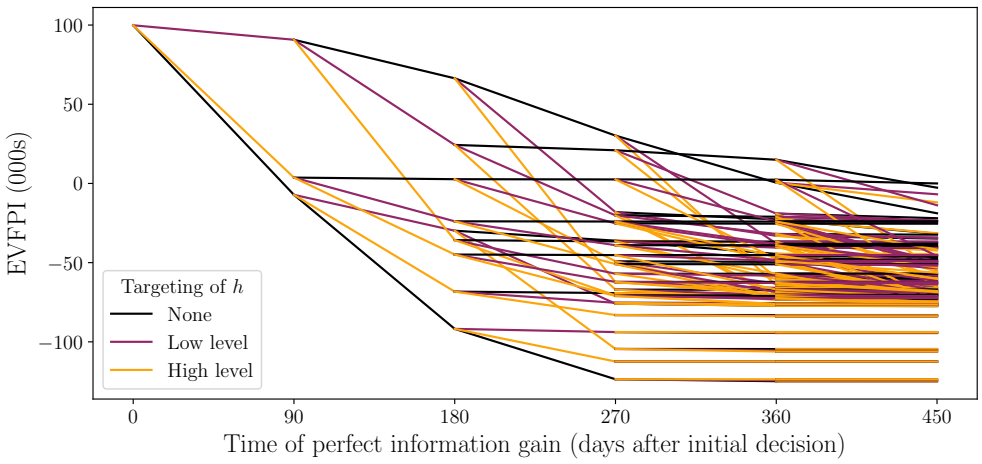


Figure 6.8: **Expected value of future perfect information (EVFPI) for different decisions.** We calculate the EVFPI over time. We assume that the value on the x-axis is the point in time at which perfect information is gained (hence truly optimal decisions are made thereafter) and the EVFPI on the y-axis is conditional on the decisions that were made before this point. Colours represent the different interventions that can be chosen at each decision point. The final point along the x-axis represents a situation where perfect information is obtained after the final decision point, hence it can not be used to inform decisions and thus we rely only on prior information. Before we obtain perfect information, we assume that h_0 and h_s are unknown, with priors $h_0 \sim Normal(0.2, 0.05)$ and $h_s \sim Normal(0.05, 0.01)$. All other parameters are assumed known with values given in Table 6.1.

be some flexibility in the time taken to resolve uncertainty, it is necessary to estimate this delay to within certain intervals in order to make optimal decisions during early stages of the outbreak.

6.3.3 Unknown effect of interventions

We incorporate uncertainty regarding the effect of our targeted interventions on h and demonstrate how this can be used to portray further, useful information to decision makers in an interpretable way. So far, we have assumed that targeting the healthcare-seeking probability results in an increase in h via Equation 6.1. The rate of increase depends on Δ_h, which we have set at 0.01 for low level targeting and 0.03 for high level targeting. We introduce uncertainty into this parameter, by assuming that both levels of intervention could be between 50% less effective up to 50% more effective than expected. In order to clearly portray the effect of such uncertainty, we discretise it into three models: 50% effective, 100% effective and 150% effective. Depending on the weight we place on each model, representing our prior belief as to

which model is most likely, the optimal course of action may change (Figure 6.9). We first assume a passive AM approach, relying solely on prior information to make initial decisions.

If we place all the weight on the 100% model (Figure 6.9; top corner), we are completely confident that Δ_h is equal to what we have defined it to be, which is equivalent to previous sections. In this case, high level targeting of h from the start appears optimal, as this area of the graph is shaded yellow. If the majority of the weight is placed on either the 50% or 100% models, that is, close to the top or left corners of the graph, we see a similar result. However, if there is a significant chance that interventions will be more effective than expected, represented by the 150% model and right corner of the graph, then taking a more conservative approach, targeting h at a low level initially, would be recommended. Furthermore, we find that the penalty from making the 'wrong' initial decision is not symmetric. Choosing to target h at a low level, when high level targeting would be recommended under the prior, results in approximately 25% less of an increase in the expected number of deaths compared to the opposite scenario (Figure 6.9; right-hand panel). Hence, low level targeting of h may be a more appropriate option under such uncertainty. This is reinforced by the fact that, if we place equal weight across all three models (centre of the graphs), the optimal initial decision is to implement low level targeting of h.

Finally, we use an active AM approach to aniticipate the resolution of uncertainty in the effect of interventions on h. We assume that uncertainty is resolved after 90 days, however only if an intervention is implemented. Hence, this represents the use of experimentation: we can only resolve uncertainty in the effect of a control by implementing that control and monitoring it. We analyse the EVFPXI for the uncertainty in interventions (that is, h_0 and h_s remain uncertain). We find that resolving uncertainty in the effect interventions through experimentation can reduce the expected number of deaths by up to approximately 14,000 (Figure 6.10; left-hand plot). The benefit of experimentation is most pronounced when we have a polarised belief regarding the efficacy of interventions (strong belief for 50% and 150% models), with a slightly higher probability of interventions being over-effective than under-effective. If we place all the weight on a single model (corners of the plot), we are essentially assuming no uncertainty, thus the benefit falls to zeros. Similarly, if there is very little chance of the interventions being over-effective (left-hand edge), the benefit of resolving uncertainty is very low, since it is less likely we will overload the healthcare system.

We also calculated the EVPXI measure assuming resolution in h_0 and h_s only (Figure 6.10; right-hand plot). We found that benefit of resolving uncertainty in

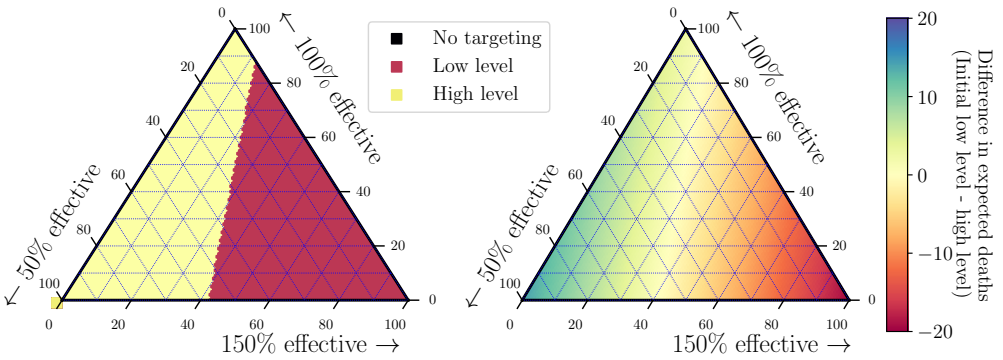


Figure 6.9: **Effect of uncertain intervention efficacy on optimal initial decisions.** We assume that interventions targeting h are either 50% less effective than expected, the same as expected or 50% more effective that expected (defined by the value of Δ_h). We vary the weight we place on each model (the strength of our belief in each model), specified by the value on each axis, summing to 100%. Thus, the top corner represents 100% weight on the 100% effective model, the left corner 100% on the 50% model and the right corner 100% weight on the 150% model. Away from the corners, the weights are split between multiple models, with the centre of the graph representing equal weight on all three models. We record the initial action that leads to the lowest expected number of deaths (left) and the difference in the expected number of deaths between implementing low level and high level targeting of h in the initial intervention phase (right). Expectations are calculated based on prior information only. We assume that h_0 and h_s are also unknown, with priors $h_0 \sim Normal(0.2, 0.05)$ and $h_s \sim Normal(0.05, 0.01)$. All other parameters are assumed known with values given in Table 6.1.

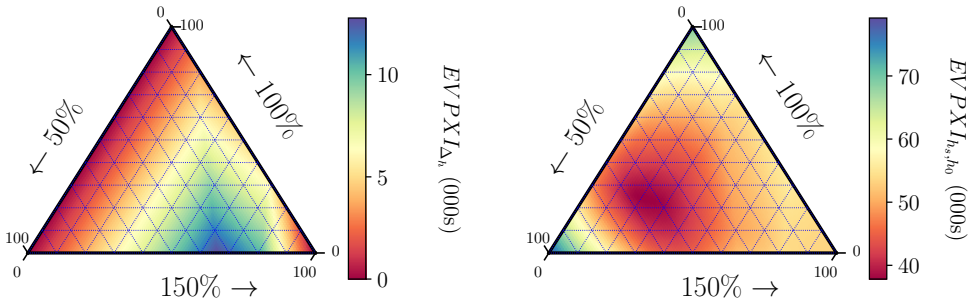


Figure 6.10: **EVFPXI for resolution of uncertainty in effect of interventions and current healthcare-seeking behaviour.** We assume that interventions targeting h are either 50% less effective than expected, the same as expected or 50% more effective that expected (defined by the value of Δ_h). We vary the weight we place on each model (the strength of our prior belief in each model, summing to 100%). We calculate the EVFPXI assuming that uncerainty is resolved after 90 days. Left: uncertainty in effect of interventions (Δ_h) is resolved. Right: uncertainty in h_0 and h_s is resolved. All other parameters are assumed known with values given in Table 6.1.

these parameters is significantly greater than the benefit of resolving uncertainty in the effect of interventions on h, reducing the expected number of deaths by between 40,000 to 80,000. In this case, the greatest benefits are obtained when we are more certain about the effect of interventions (corners of the plot), since this allows for the most effective adaptation.

6.4 Conclusions and discussion

In this chapter, we have emphasised the importance of the healthcare-seeking behaviour of the population on the outcome of the epidemic. We have shown that changes in the healthcare-seeking probability of individuals with symptoms will affect the peak number of individuals requiring healthcare during the outbreak. For increases from low levels of healthcare-seeking to medium levels ($0 \leq h \leq 0.5$), we end up with a greater burden on the healthcare system. However, if the system has the capacity to accommodate this increase, the outcome of the epidemic will be greatly improved. For further increases in h ($0.5 \leq h \leq 1$), we find that the burden on the healthcare system can decrease, due to a significantly reduced R_0 early on in the outbreak. However, this depends on the proportion of 'healthy' individuals also seeking healthcare, due to having similar symptoms from a different, less serious condition. In extreme cases, the increased number of healthy healthcare-seekers may outweigh the decrease in the number of infected healthcare-seekers. Overall,

non-infected healthcare-seekers can be a significant contribution to the burden on the healthcare system, a fact that supports investment into early detection and accurate triage systems (e.g. [35]).

Changes in the tendency of individuals to seek healthcare, and the resulting change in the burden on the healthcare system, can become a serious issue if the capacity of the system is exceeded. Whilst operating at capacity allows for the most people to be admitted into healthcare, it is possible that a significant excess in demand for healthcare may cause the system to become overloaded and operate inefficiently. Hence, whilst increasing the healthcare-seeking probability of the population through community engagement can be a highly successful form of control, the amount by which it is increased is very important. Increasing h too much can lead to overloading the healthcare system, which in turn causes a sharp resurgence in the expected number of deaths.

Adaptive management can help to target h effectively, reducing the probability of overloading the healthcare system when the healthcare-seeking behaviour of individuals and effect of interventions is uncertain. From a passive AM perspective, not anticipating the resolution of uncertainty, we found that an adaptive decision process with 5 decision points at 90 day intervals reduced the expected number of deaths from the outbreak by at least 15% compared to a static approach (only a single decision point) and over 40% compared to not targeting h at all. We were also able to optimise the timing of decision points, with the best results obtained from at least two decision points during the first 180 days of the outbreak. The overall recommended policy, under passive AM, was high level targeting of h for the first 90 days, followed by reinvesting those resources into increasing the capacity of the healthcare system for the remainder of the outbreak. The early targeting of h results in a significantly reduced outbreak early on. On average, this results in a lower burden on the healthcare system and thus fewer deaths overall. However, in some cases the high level targeting of h will cause the healthcare system to become overloaded and thus result in a less desirable outcome. This occurs if the original healthcare-seeking probability of the population (h_0) is higher than expected, the proportion of non-infected individuals in the population with similar symptoms (h_s) is higher than expected or if the effect of targeted interventions (Δ_h) is more than expected. However, if we do not expect to resolve the uncertainty in these parameters, the benefit of increasing h quickly at the start of the outbreak outweighs the possible negative effects of overloading the system.

We obtain very different results when using an active AM approach, anticipating uncertainty resolution. Using the EVFPI measure introduced in Chapter 4

(Equation 4.9), we were able to analyse the effect that resolving uncertainty in the parameters at some point in the future will have on the optimality of different initial decisions. We found that low level targeting of h early on in the outbreak allows for significantly greater improvements of control in light of new information compared to high level targeting. This is because, once the healthcare-seeking rate has been increased through targeted intervention, it can not be reduced again. Using high level targeting, we achieve a high healthcare-seeking probability after a single phase of intervention. Even with new information after this phase, we can not optimise the value of h further. However, using low level targeting, the healthcare-seeking probability is not increased so dramatically during the first control phase. Hence, in subsequent phases, both continued targeting or no targeting is an option. This allows greater adaptation in light of new information. Hence, if we are expecting to resolve uncertainty during the outbreak, an initial stage of low level targeting is the recommended course of action. Following this active AM approach, we could reduce the expected number of deaths by almost 100,000 individuals (60%), if uncertainty is resolved within the first 90 days.

The use of the EVFPI measure also allowed for a clear portrayal of the cost of delaying the resolution of uncertainty, or equivalently, the benefit of resolving uncertainty earlier. Over the first 90 days, implementing low level targeting of h allows for a slow depreciation of the value of monitoring, of approximately 10,000 deaths. However, as time progresses the value of monitoring depreciates faster. Between 90 to 180 days after detection, not targeting h allows for the best adaptation in light of new information, but we increase expected deaths by another 20,000. In the subsequent 90 days, this increases by another 40,000. If we do not expect to resolve uncertainty within the first 270 days of the outbreak, the value of monitoring becomes negligible, since uncertainty resolution occurs too late in the outbreak for control adaption to have a significant effect. If this is the case, raising h to a high level quickly, as recommended by the prior information, is the optimal decision. This is important information for decision makers, who may be need to allocate limited resources during the early stages of an outbreak to either monitoring or control.

We were able to incorporate uncertainty in both the current healthcare-seeking behaviour (h_0 and h_s) and the effect of control interventions (Δ_h) into our AM approach. We found that doing so also encourages implementing low level targeting of h as opposed to high level, unless we have a strong belief that the effects of intervention will not be more than expected. This is due to the fact that the cost of over-targeting h, causing an overloaded healthcare system, is greater than the cost of under-targeting h and not reaching capacity. We also assessed the importance of resolving uncertainty

in the effect of interventions, in comparison to resolving uncertainty in h_0 and h_s, using the EVFPXI measure. If the effectiveness of interventions is between 50% to 150% of what we expect, resolution of uncertainty in h_0 and h_s is significantly more important than resolving uncertainty in effectiveness. The exact values depend heavily on our prior belief regarding the efficacy of interventions. If we think it is unlikely that the effect of interventions will be greater than expected (low weight on 150% efficacy model), there is very little value to resolving uncertainty in the effect of interventions, since we will likely opt for high level targeting of h. However, if there is a significant probability that the effect will be greater than expected, the benefit of resolving this uncertainty is increased. Overall, in this scenario we would recommend allocating more resources to ascertaining the current healthcare-seeking behaviour of the population than the effect of control interventions. However, this does provide another example of how experimentation of control with an unknown effect can improve the outcome of management overall.

There are a number of limitations of this work. First, the definitions of the healthcare system capacity and penalty for overloading the healthcare system are overly simplistic. We have defined the capacity of the healthcare system in terms of the maximum number of people that can be within healthcare at one time. This applies well to bed capacity, however does not take into account the capacities of resources, such as protective gear, or medicines, which would depend on the total number of patients over time. The penalty for overloading is implemented as a closure of the healthcare centres for a fixed period of time. In reality, it is unlikely that this would occur. This could be implemented in a number of other ways, including a reduced admission rate, increased fatality rate or increased nosocomial infection rate. The penalty for overloading the healthcare has a significant effect on the optimisation of control, thus should be carefully formulated for specific problems.

The effect of targeted interventions on h could also be defined in a number of different ways. We assume that the effect is greatest immediately after intervention, then levels off over time. However, it may be that interventions take some time to have an effect, thus leading to a slower increase in h at first. In this case, a sigmoid function may be more appropriate [144]. We have also assumed that the healthcare-seeking rate remains the same after interventions are lifted. However, as the outbreak progresses, it may be that the healthcare-seeking rate increases without intervention due to increased awareness of the disease [144]. Finally, we have assumed that the healthcare-seeking rate can not be decreased, thus interventions are not reversible. However, once community engagement is ceased, it is possible that healthcare-seeking falls again. Whilst we have not explored these effects here, they

could be included in the AM framework as different models of system behaviour.

Finally, we have not considered the effect of an unknown transmission rate or vaccination with an unknown efficacy, as explored in the previous chapter. Since the transmission rate has a significant effect on the number of infections, we would expect this play an important role in the level of burden on the healthcare system. If this parameter is uncertain, it should be included and averaged over in the calculation of expectations within the AM framework. The resolution of uncertainty in β may also be beneficial, something we could assess using the same EVFPXI analysis we have used here. The implementation of a mass vaccination campaign with unknown efficacy has already proven to be non-trivial decision in the previous chapter. The addition of a changing healthcare-seeking probability h would add to that complexity, since it significantly changes the vaccine efficacy required to have a positive effect. Hence, an intervention that targets h would effect the optimal monitoring and thresholds for vaccine efficacy that we calculated in the previous chapter. As such, it is necessary to model such interventions together to account for these interactions.

Whilst the analyses in this chapter have been based on a simplified system, we believe the methods used are highly relevant to the management of real-world outbreaks. For example, in the ongoing COVID-19 outbreak in the UK, it may be necessary to implement an incremental strategy relaxing the restrictions of the lockdown. However, the exact effect of such relaxation on contacts within the population and thus the transmission of the disease may be unknown until such measures have been tried. Furthermore, the burden on the UK healthcare system, including hospital capacities and the availability of equipment, is an important factor to consider before relaxing current lockdown measures. We believe that active AM could be an extremely helpful tool in a scenario such as this. Furthermore, these results contribute to analyses in the literature regarding the use of AM to provide easily interpretable information to decision makers [139], identify important uncertainties (those that, when resolved, lead to the most benefits) [10, 123, 126] and highlight the time sensitivity of monitoring and control actions at the start of an outbreak [10, 23].

Chapter 7

Conclusions and future work

The aim of this thesis has been to motivate the use of the AM framework in the management of epidemics. Although AM has been widely studied in the context of ecology and resource management for several decades [44, 46], applications in epidemiology are extremely rare [11, 51]. Whilst not all management contexts are appropriate for AM [42, 67], we believe that the management of epidemics is. First, there is a high level of uncertainty involved, especially at early stages of an epidemic. Furthermore, much of this uncertainty is epistemic, relating to unknown dynamics of spread and effects of control. Second, we often have access to real-time information collected from monitoring the outbreak, such as daily reported cases or deaths, which can be used to reduce uncertainty in the system as the outbreak progresses. Finally, the impact of the outbreak, whether it be represented as a financial cost or the number of lives lost, is highly sensitive to the control interventions that are implemented throughout. We have supported this with an exploration of AM applied to epidemic control, covering a range of scenarios that involve different sources of uncertainty, objectives of management and forms of control. We have analysed in detail the contribution of certain components of the AM framework, such as the optimisation approach used and how we model the resolution of uncertainty obtained from monitoring. We have demonstrated the utility of AM in providing important information to decision makers that can be used to lessen the fallout from an epidemic.

Throughout this work we have largely focused on the use of active AM. In Chapter 3, we clarified the meaning of the term *active* AM: referring to the explicit anticipation of uncertainty resolution during the optimisation process. This differs to *passive* AM, under which we make decisions assuming that uncertainty will remain the same in the future. Similar analyses exist in the literature [58, 137], but not applied to

epidemiological interventions. We showed that actively anticipating the resolution of uncertainty in the future can lead to different decisions now, ultimately improving the outcome of control. In this case, we assessed the ability of a vaccination campaign, with unknown vaccine efficacy, to reduce the cost or duration of an outbreak. We assumed that, if a campaign was implemented, it could be monitored in order to resolve uncertainty regarding vaccine efficacy. This constitutes the *experimentation* [48] of control in order to resolve uncertainty. Using active AM, we observed that implementing a vaccination campaign immediately and monitoring the efficacy of the vaccine allowed for improved management overall. Using a passive or non-AM approach, we are unable to recognise this, opting for a suboptimal policy of not vaccinating immediately, thus removing our ability to resolve uncertainty. Finally, an active AM approach allowed us to analyse other factors that could be extremely useful to decision makers and further improve outcomes, such as the length of time to wait between decisions and characteristics of the vaccination campaign.

An essential component of active AM is the ability to predict how monitoring will result in the resolution of uncertainty in the future. In Chapter 4, we analysed the effect of this component in detail. We introduced and analysed three methods of predicting uncertainty resolution: a perfect information method, which assumes complete resolution of uncertainty, an abstract method, which assumes partial resolution but does not depend on the state of the epidemic, and a mechanistic method, which aims to model the monitoring process directly. We used these methods in conjunction with active AM, to assess the use of a vaccination campaign to minimise the cost of an epidemic with unknown epidemiological parameters. We observed that, under all three methods, an initial phase of monitoring before implementing a vaccination campaign was recommended. Using a passive or non-AM approach, we would make the suboptimal decision to vaccinate immediately. Whilst all three methods of predicting uncertainty resolution led to the same initial decision, they provided varying degrees of information regarding the optimisation of monitoring and control. The perfect information method is useful for providing an upper bound for the benefit obtained from resolving uncertainty, however is unable to advise on the optimal use of monitoring resources or timing of control. It is also useful for identifying which uncertainties are most valuable to resolve, if there is more than one, allowing for targeted monitoring. The abstract method can provide useful insight into 'how much' uncertainty resolution is required in order for monitoring to be beneficial, however lacks a basis in the real world. Its detachment from the state of the epidemic also makes it unreliable for optimising the allocation of monitoring resources and timing of control. The mechanistic method, whilst computationally demanding, provides the most useful information for decision makers. Using this

method we were able to assess the amount of monitoring required, as a number and size of cross-sectional samples of the population, testing for infection. Furthermore, we were able to optimise the timing and allocation of resources to each sample and recommend if and when a vaccination campaign should be implemented. Overall, developing a mechanistic model of uncertainty resolution to be used within the AM framework can help to significantly improve the management of an epidemic.

The analysis from Chapter 4 also highlighted that even without experimentation, an *active* AM approach is incredibly important. In this scenario, monitoring and resolving uncertainty in the epidemiological parameters can occur with or without the implementation of a vaccination campaign. Furthermore, the efficacy of the vaccine was assumed to be known, hence experimentation was not required to resolve this. However, an active approach to uncertainty resolution still resulted in a different initial decision compared to a passive approach. This is because some decisions transition us into states from which we are better able to adapt to new information than other states. For example, an initial decision not to vaccinate transitions us into a state where we have not committed to a vaccination campaign, but have allowed the epidemic to spread unhindered for a short amount of time. Conversely, an initial decision to vaccinate transitions us into a state where we have committed to a vaccination campaign, but the epidemic will have spread slightly less during this time. In light of new information, the former allows us to avoid a vaccination campaign and the costs it incurs altogether, whilst the latter does not, since a vaccination campaign has already been started. Only using an active AM approach can we recognise such effects. Finally, an active AM approach is also necessary to further optimise the implementation of monitoring and control. Thus, even without explicit experimentation, active AM is a useful tool.

A significant barrier to the use of AM, especially active AM, is the inherent complexity of both the implementation of such methods and the results we obtain from them. The latter makes it extremely difficult for decision makers to make use of the information AM can provide. In Chapters 3 and 4 we used highly simplified models to exhibit some of the useful information that can be obtained from an active AM analysis. In Chapters 5 and 6 we used a more complex scenario, approaching a real-world context, to demonstrate how the ideas and methods we have introduced can be used to extract easily understandable, but important, information for decision makers.

We introduced the new scenario in Chapter 5: we wish to analyse an Ebola-like disease, based on models used in the literature [144], incorporating the use of both mass vaccination and the establishment of healthcare centres. We introduced the idea

of 'risky behaviour', exhibited by those who have been vaccinated. We found that such behaviour can reduce the effectiveness of a mass vaccination campaign, even resulting in an increased number of deaths through vaccination if vaccine efficacy is low. In light of this, we introduced a new objective that can reflect the risk-averse nature of decision makers: we assume that a mass vaccination campaign will only be implemented if the probability of increasing the number of deaths through vaccination is below a specified level ϵ. By formulating a mechanistic model of a vaccine trial, we used active AM to develop time-dependent thresholds for the estimates of efficacy obtained from the trial. These thresholds can be used to trigger the implementation of a mass vaccination campaign if the estimate of efficacy is above the threshold. We also showed the effect of having uncertainty in both the epidemiological and control parameters: uncertainty in the transmission rate can significantly effect the requirements for monitoring vaccine efficacy, possibly rendering it irrelevant. Furthermore, the results of monitoring and resolving uncertainty in the transmission rate can affect the resolution of uncertainty in the vaccine efficacy, even if results from the vaccine trial have not changed. We used both an abstract and mechanistic model of uncertainty resolution for the transmission rate, to develop state- and time-dependent thresholds for the estimates of vaccine efficacy. This also highlighted the limitations of using a convenient, abstract model of uncertainty resolution as opposed to a computationally intensive, mechanistic model.

In Chapter 6 we analysed the effect that the healthcare-seeking behaviour of the population has on our Ebola-like disease model. We introduced a capacity on the healthcare system and a penalty for exceeding that capacity, in the form of a temporary shut down of healthcare centres. We introduced a new control intervention: community engagement, resulting in an increase in the healthcare-seeking probability of the population. We found that implementing such an intervention can significantly reduce the number of deaths from the outbreak. However, if there is uncertainty surrounding the current healthcare-seeking behaviour, existence of non-infectious healthcare-seekers and effect of control, such interventions can result in overloading the healthcare system, leading to more deaths. We applied AM to this scenario and showed that it can help to optimise the implementation of interventions targeting the healthcare-seeking probability, maximising the benefit and reducing the chance of overloading the healthcare system. We again showed that a passive AM approach, whilst superior to a static, non-AM approach, can lead to suboptimal decisions compared to an active AM approach. Under active AM, we recognise that a more conservative intervention initially allows for better adaptation of control in the future. We also exhibited the use of the EVFPI measure to clearly portray the benefit of resolving uncertainty quickly, or the cost of delaying, to decision makers. In addition,

we used the EVPXI measure to identify which uncertainties are most beneficial to resolve, allowing for efficient allocation of monitoring resources if necessary. Finally, the incorporation of uncertainty in the effect of these interventions, which can only be resolved if the intervention is implemented, provides a realistic example of active experimentation that is relevant to real-world outbreaks.

This work has provided motivation and a foundation for the use of AM in the management of epidemics. We have demonstrated the ability of AM to address several areas of interest that are often considered in the literature: the balance of monitoring and control [141, 143, 153], the optimal allocation of resources [29, 139], efficient, targeted monitoring plans [7, 15, 27], the identification of control 'triggers' [25, 28, 29, 152] and resolving uncertainty in selected parameters to improve control [10, 56, 123, 124]. A framework that allows analysis of all these factors would be a great asset to decision makers.

Future directions for this work are wide ranging, however we believe a significant focus should be on the application of this framework to specific scenarios. This is highly non-trivial, especially in three areas: first, the development of accurate, disease-specific models of system behaviour and uncertainty resolution. This embodies much of the work already performed by mathematical epidemiologists, providing a wealth of knowledge to make use of. However, selecting which models to use, or developing new models, can be a daunting task. We propose a possible solution to this through the combination of ensemble modelling with AM. Ensemble modelling is a modelling approach in which multiple models are used to make predictions that are then combined, according to some weighting process, into a single aggregated prediction (e.g. [16, 154]). It has been shown to provide better predictions overall than individual models alone [32, 37]. This could be incorporated into the AM framework, allowing the weights to be assigned and updated iteratively as the outbreak progresses.

Second, implementing AM in realistic settings is computationally extremely difficult. Standard methods, such as those used throughout this thesis, involve the use of Markov decision processes (MDPs) and stochastic dynamic programming (SDP). However, such methods require a discretised state space and set of possible actions. In the context of epidemic control, the space of possible epidemics that could occur, as well as the controls that could be implemented, is effectively infinite and requires incredibly fine discretisation in order to provide relevant results. This quickly becomes computationally intractable using traditional methods [14, 155]. The development of more efficient solutions to such problems is ongoing, with a recent move into areas of reinforcement learning [14, 156]. We propose the use of such methods in conjunction with AM to allow for application to more complex

systems.

Third, interpreting the results obtained through an AM procedure is a specialised task. In this work, we have restricted ourselves to two sources of uncertainty to allow visualisation of results and state-dependent recommendations. However, in the case of multiple sources of uncertainty and separate rates of uncertainty resolution, this becomes a difficult task. This is an issue, since results need to be translated into a form that decision makers can easily understand and make use of. This has begun to be addressed in some areas [14], though not yet in conjunction with the AM framework.

Overcoming these difficulties should be a focus of future work involving the AM framework, especially in peace-time. However, in spite of these barriers, we believe that the methods we have used in this thesis are immediately implementable and useful for the ongoing COVID-19 outbreak. We hope to use already developed models that accurately represent and predict the dynamics of spread to assess the benefit of adaptive relaxation of lockdown measures that are currently in place across the UK. Using measures such as the EVFPI and EVPXI within an active AM approach, we can quantify the benefit of experimental, staged relaxation, inform optimal timing, identify important sources of uncertainty and provide triggers for lockdown reinstation based on observable quantities such as hospital or ICU admissions.

In summary, this thesis has provided an in depth analysis of the use of the AM framework in the context of epidemiological interventions. We have explored several different components, including the use of active or passive optimisation and the method of predicting uncertainty resolution, providing valuable insight into the effects and benefits of different methods within the framework. We have motivated the use of active AM, explicitly incorporating the future resolution of uncertainty through mechanistic models of monitoring, in the control of epidemics. We believe the practical implementation of such an approach could greatly improve the outcome of epidemics in the future.

Appendix A

Appendix to Chapter 3

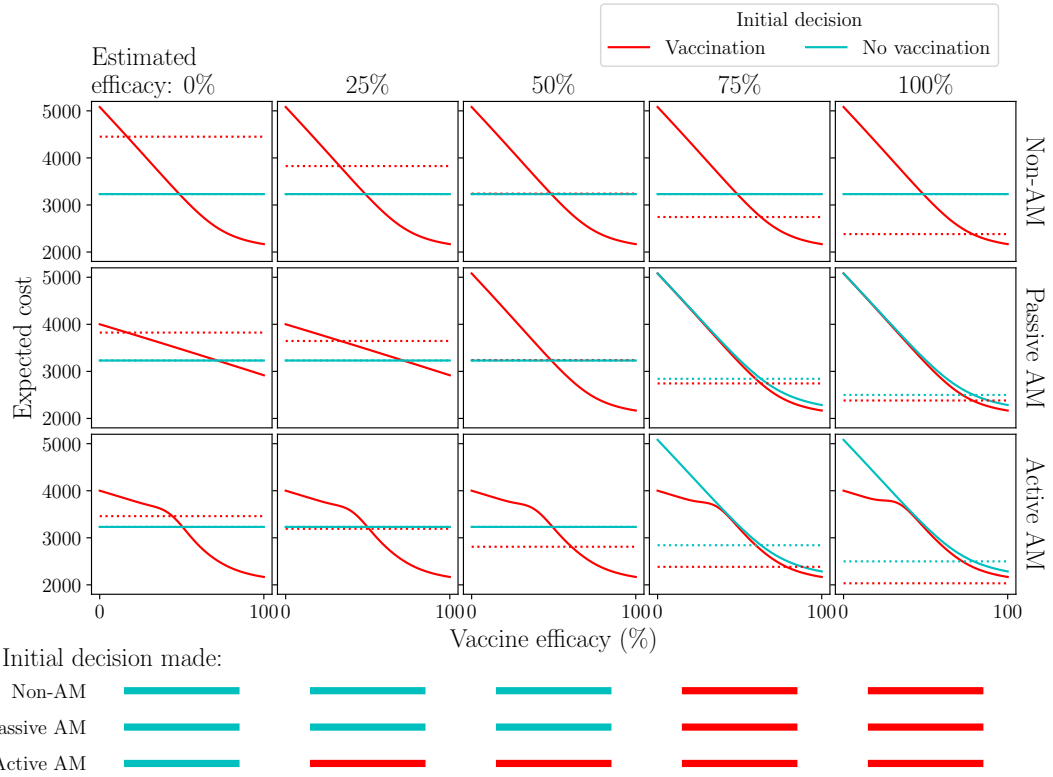


Figure A.1: **Example effect of prior information on the expected cost of the outbreak given an initial decision to vaccinate or not.** We set $x_0+y_0 = 4$ and vary the estimate of vaccine efficacy (the mode of the distribution $\frac{x_0}{x_0+y_0}$) across columns. Rows 1-3: predicted outbreak cost over vaccine efficacy, given an initial decision to vaccinate (red) or not (blue), for different prior estimates of efficacy, as viewed under a non-AM, passive AM or active AM approach respectively. Bottom row: initial decision made under each approach, for different prior estimates of efficacy: vaccinate (red) or don't (blue). Epidemiological and vaccination parameters are set to those in Table 3.1: Scenario 1.

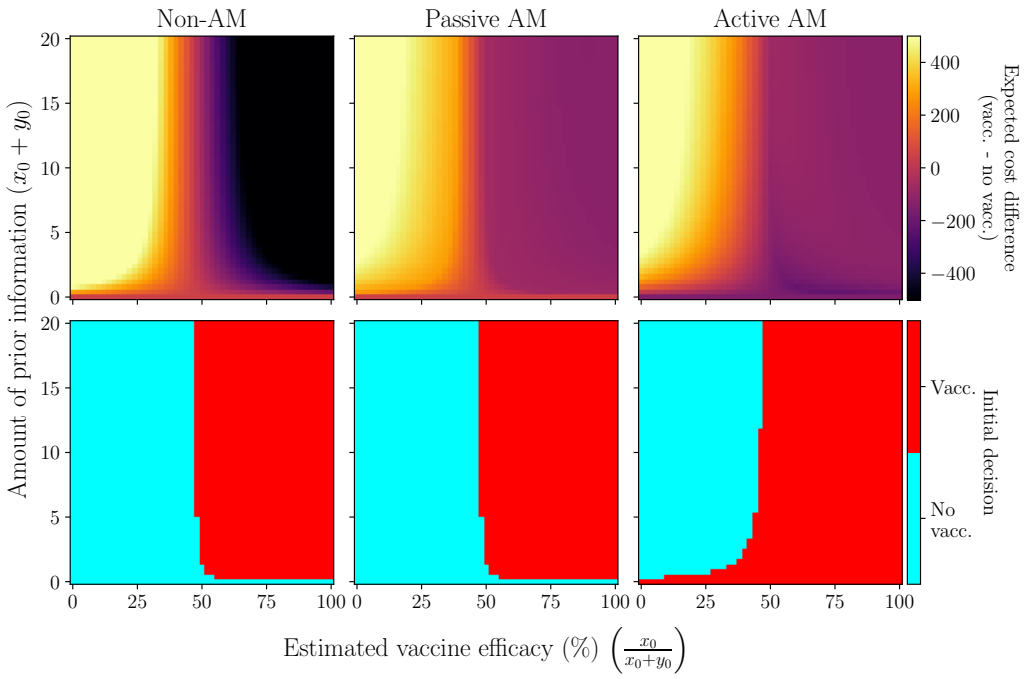


Figure A.2: **Scenario 1: Initial decision made under each approach given different prior information.** We define prior information using a Beta(x_0+1, y_0+1) distribution and vary the estimated efficacy (the mode of the distribution; $\frac{x_0}{x_0+y_0}$) and the amount of information supporting this estimate ($x_0 + y_0$). Top row: difference in expected cost between vaccinating initially or not, as viewed under each approach. Bottom row: initial decision made under each approach: vaccinate (red) or not (blue). Epidemiological and vaccination parameters are set to those in Table 3.1: Scenario 1.

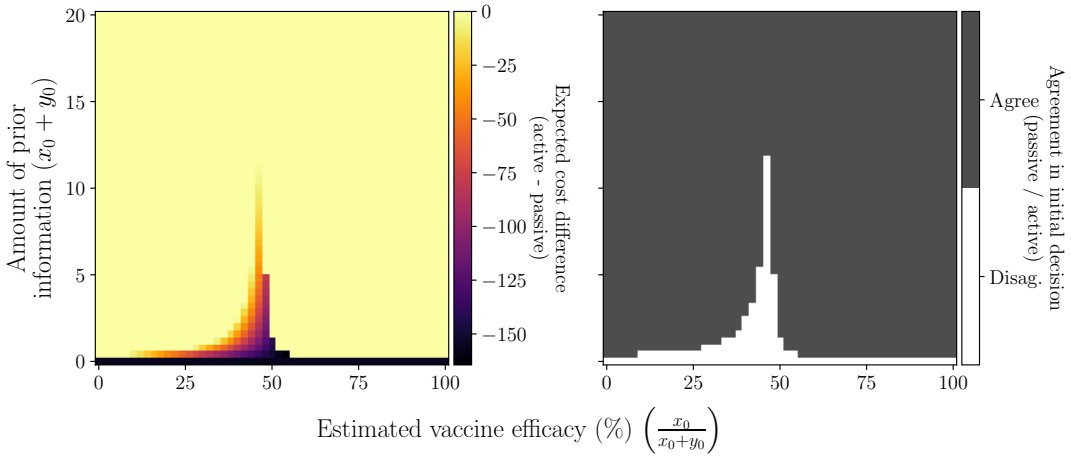


Figure A.3: **Scenario 1: Comparison of initial decision made between active and passive AM given different prior information.** We define prior information using a Beta$(x_0 + 1, y_0 + 1)$ distribution and vary the estimated efficacy (the mode of the distribution; $\frac{x_0}{x_0+y_0}$) and the amount of information supporting this estimate $(x_0 + y_0)$. Left panel: difference in expected cost under active AM compared to passive AM. Right panel: agreement in initial decision between passive AM and active AM. Epidemiological and vaccination parameters are set to those in Table 3.1: Scenario 1.

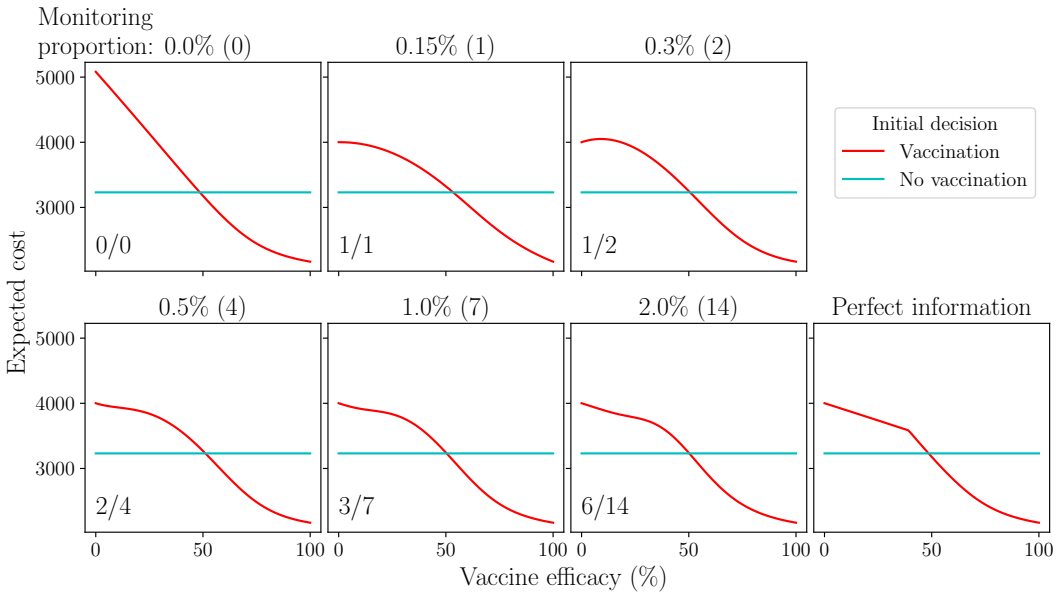


Figure A.4: **Scenario 1: effect of monitoring proportion on the predicted outbreak cost given an initial decision to vaccinate or not.** Predicted outbreak cost over vaccine efficacy, given an initial decision to vaccinate (red) or not (blue), for different monitoring proportions (ρ; Table 3.1). The number of monitored vaccinations is given in brackets beside the proportion. The required number of successful vaccinations from the total number monitored in order to make a decision to vaccinate is shown in the lower left corner of each panel. The far right panel assumes perfect information is obtained after day t^*, that is, we will know the true vaccine efficacy exactly when making the final decision. Epidemiological and vaccination parameters are set to those in Table 3.1: Scenario 1.

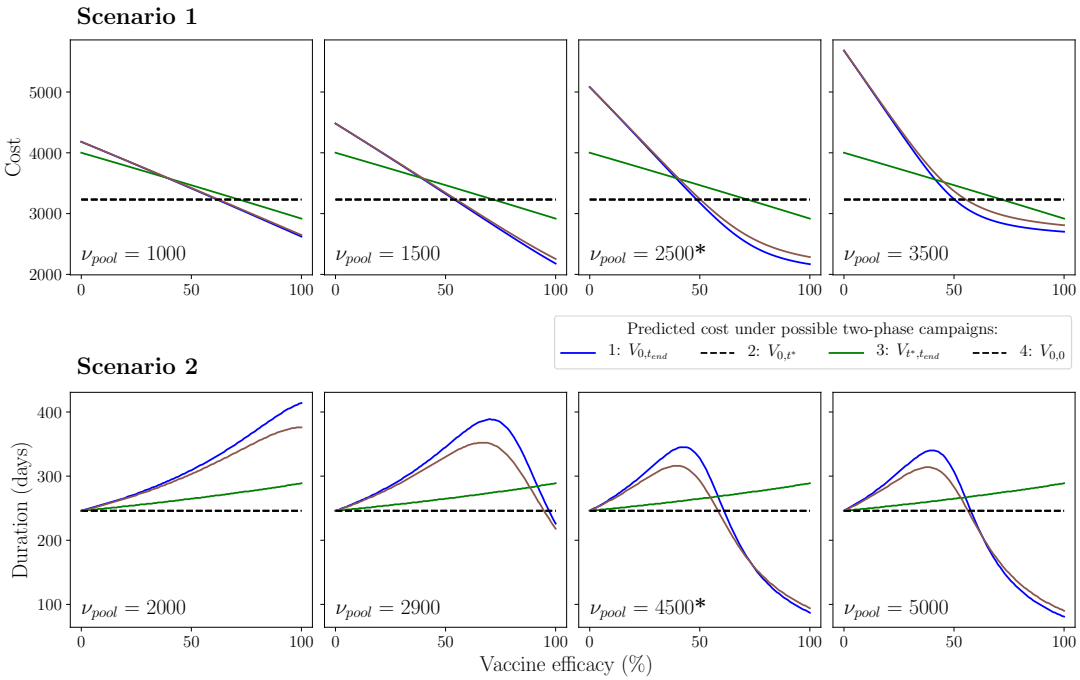


Figure A.5: **Effect of vaccine pool size on campaign performance - Scenarios 1 and 2.** All other parameters are fixed to the values given in Table 3.1. Asterisks identify the default value for the vaccine pool size used in each scenario.

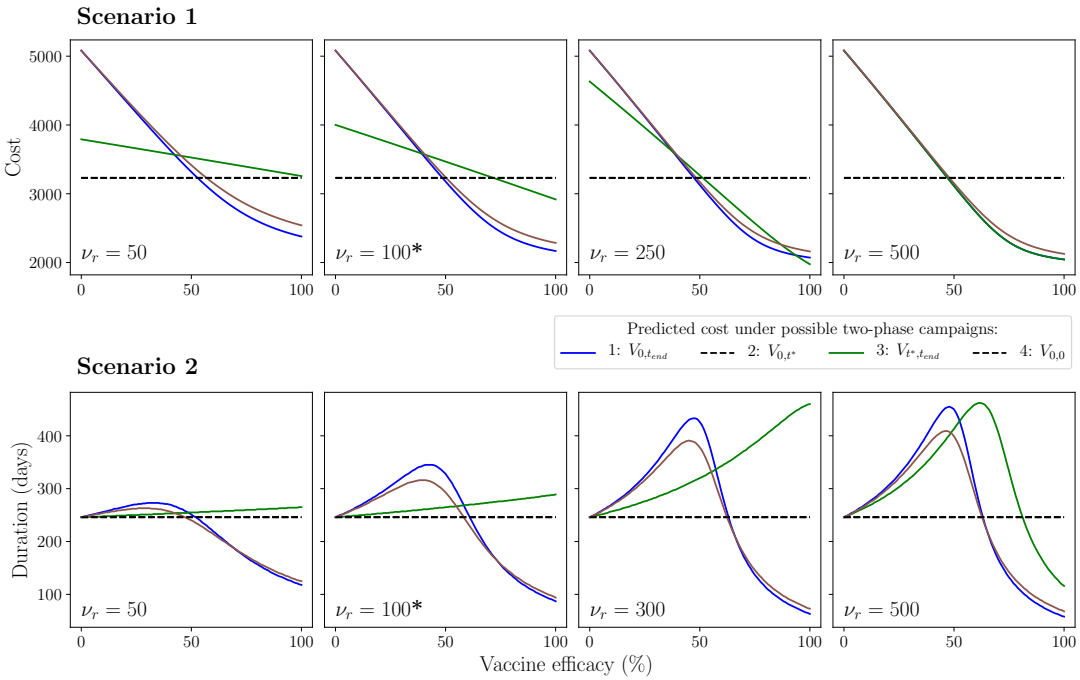
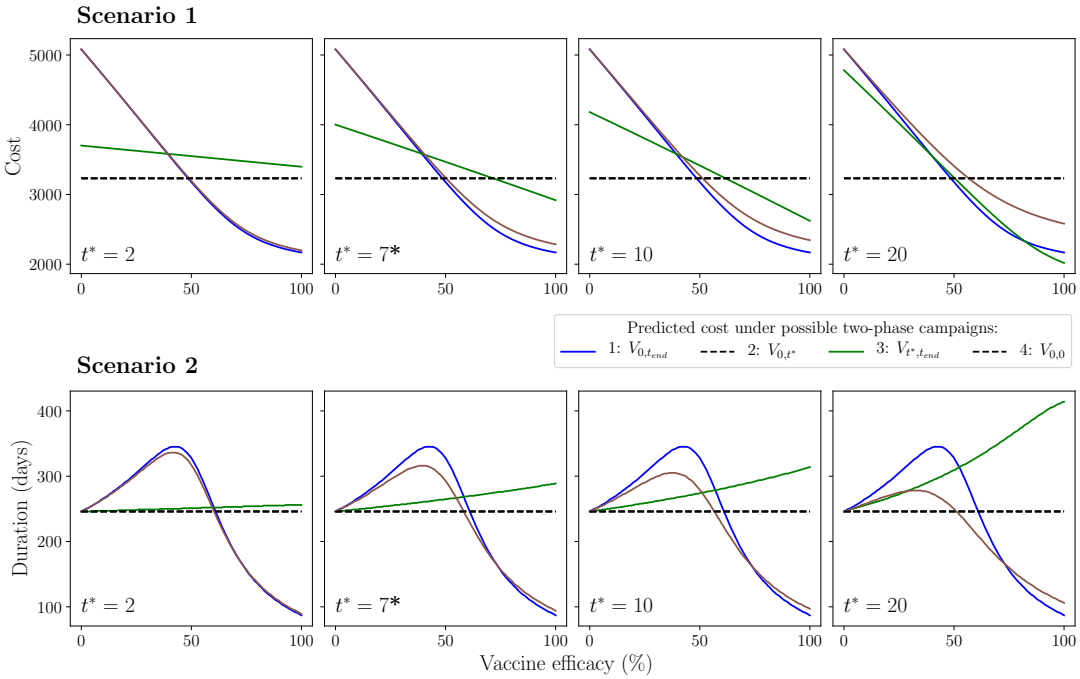


Figure A.6: **Effect of the daily vaccine rate on campaign performance - Scenarios 1 and 2.** All other parameters are fixed to the values given in Table 3.1. Asterisks identify the default value for the daily rate used in each scenario.



S7 Fig. Effect of the value of t^* on campaign performance - Scenarios 1 and 2. All other parameters are fixed to the values given in Table 3.1. Asterisks identify the default value for t^* used in each scenario.

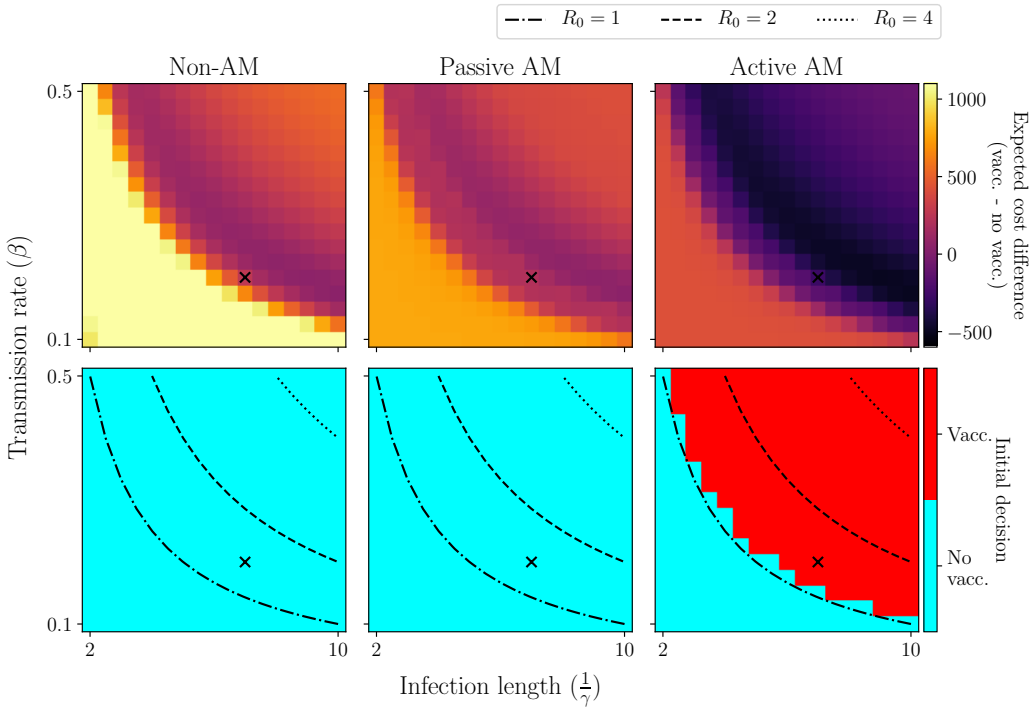


Figure A.7: **Scenario 1: Initial decision made under each approach, varying epidemiological parameters.** We vary the epidemiological parameters describing transmission (β) and recovery/removal (γ). Top row: difference in expected cost between vaccinating initially or not, as viewed under each approach. Bottom row: initial decision made under each approach: vaccinate (red) or not (blue). Black crosses represent the default values used in scenario 1 (Table 3.1). Lines of constant R_0 are identified with black lines.

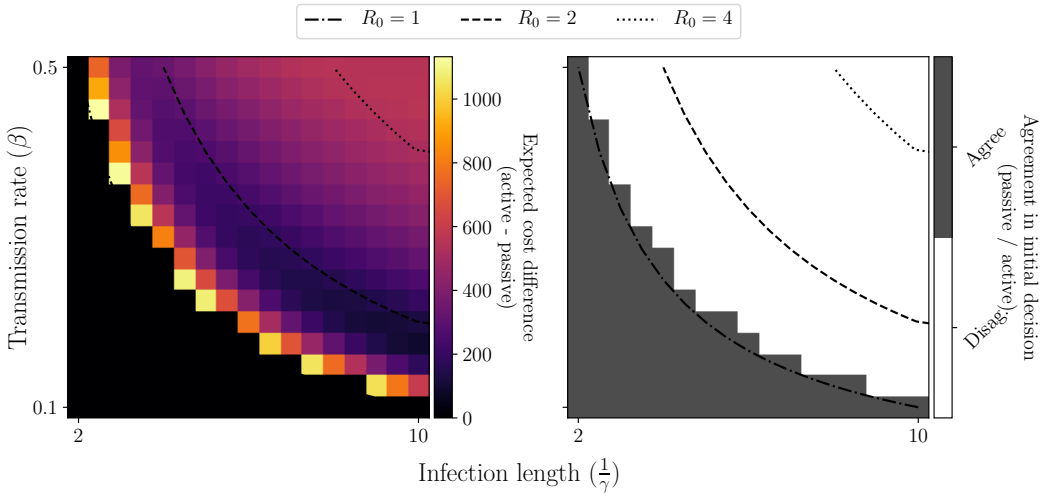


Figure A.8: **Scenario 1: Comparison of initial decision made between active and passive AM given different epidemiological parameters.** We vary the epidemiological parameters describing transmission (β) and recovery/removal (γ). Left panel: difference in expected cost under active AM compared to passive AM. Right panel: agreement in initial decision between passive AM and active AM. Black crosses represent the default values used in scenario 1 (Table 3.1). Lines of constant R_0 are identified with black lines.

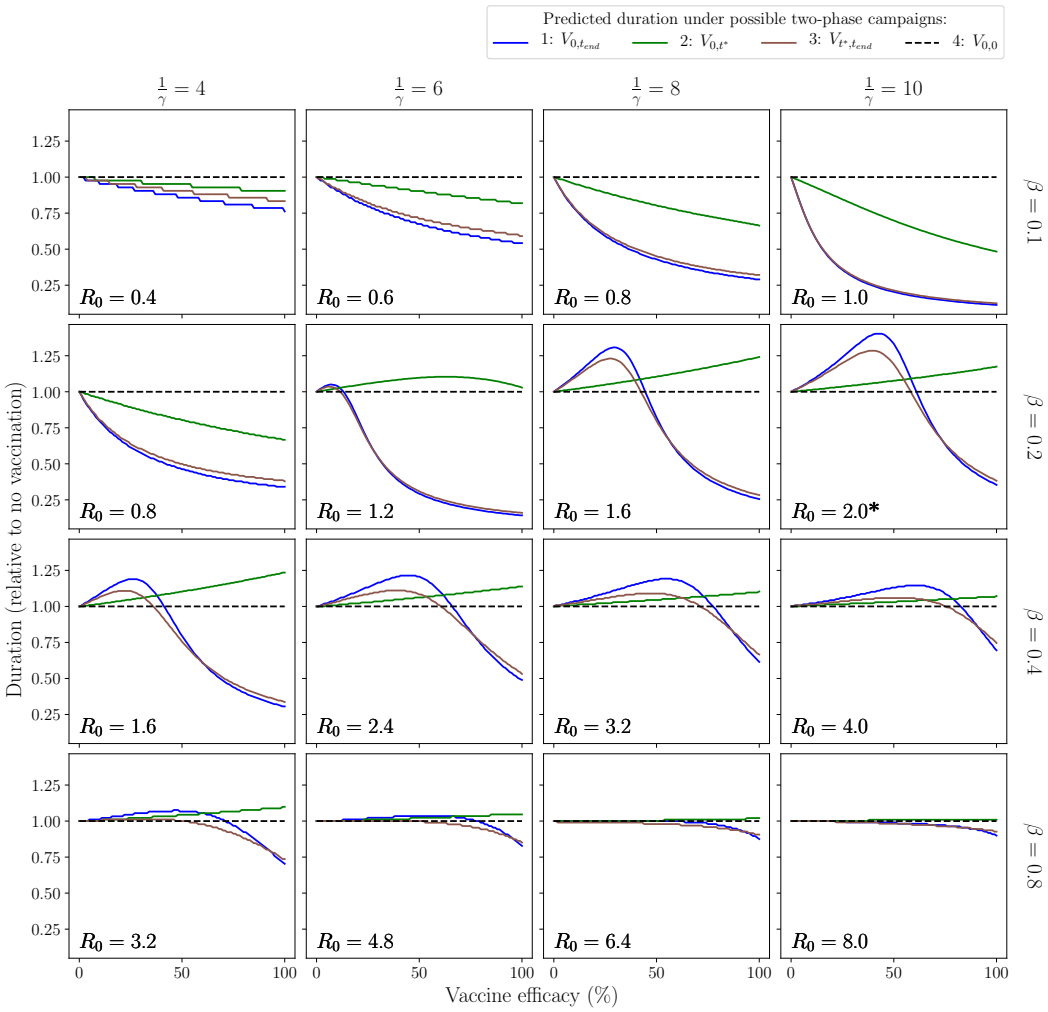


Figure A.9: **Effect of epidemiological transmission and recovery rates on campaign performance - Scenario 2.** All other parameters are fixed to the values given in Table 3.1. The asterisk identifies the default combination of transmission and recovery rates used in scenario 2.

Bibliography

[1] W O Kermack and A G McKendrick. A contribution to the mathematical theory of epidemics. *Proceedings of the Royal Society of London. Series A, Containing Papers of a Mathematical and Physical Character*, 1927. ISSN 0950-1207. doi: 10.1098/rspa.1927.0118.

[2] Matt J. Keeling and Pejman Rohani. *Modeling infectious diseases in humans and animals*. 2011. ISBN 9781400841035. doi: 10.1016/s1473-3099(08)70147-6.

[3] Roy M. Anderson and R. M. May. Infectious Diseases of Humans: Dynamics and Control. *JAMA: The Journal of the American Medical Association*, 1992. ISSN 0098-7484. doi: 10.1001/jama.1992.03490230111047.

[4] B. D. Elderd, V. M. Dukic, and G. Dwyer. Uncertainty in predictions of disease spread and public health responses to bioterrorism and emerging diseases. *Proceedings of the National Academy of Sciences*, 2006. ISSN 0027-8424. doi: 10.1073/pnas.0600816103.

[5] Robin N. Thompson and Ellen Brooks-Pollock. Detection, forecasting and control of infectious disease epidemics: Modelling outbreaks in humans, animals and plants, 2019. ISSN 14712970.

[6] Oliver Morgan. How decision makers can use quantitative approaches to guide outbreak responses, 2019. ISSN 14712970.

[7] James O. Lloyd-Smith, Sebastian Funk, Angela R. McLean, Steven Riley, and James L.N. Wood. Nine challenges in modelling the emergence of novel pathogens. *Epidemics*, 2015. ISSN 18780067. doi: 10.1016/j.epidem.2014.09.002.

[8] Michael J Tildesley, Nicholas J Savill, Darren J Shaw, Rob Deardon, Stephen P Brooks, Mark E J Woolhouse, Bryan T Grenfell, and Matt J Keeling. Optimal reactive vaccination strategies for a foot-and-mouth outbreak in the UK. *Nature*, 440(7080): 83–86, 2006. ISSN 14764687. doi: 10.1038/nature04324.

[9] Phenyo E. Lekone and Bärbel F. Finkenstädt. Statistical inference in a stochastic epidemic SEIR model with control intervention: Ebola as a case study. *Biometrics*, 2006. ISSN 0006341X. doi: 10.1111/j.1541-0420.2006.00609.x.

[10] William J.M. Probert, Chris P. Jewell, Marleen Werkman, Christopher J. Fonnesbeck, Yoshitaka Goto, Michael C. Runge, Satoshi Sekiguchi, Katriona Shea, Matt J. Keeling, Matthew J. Ferrari, and Michael J. Tildesley. Real-time decision-making during emergency disease outbreaks. *PLoS Computational Biology*, 2018. ISSN 15537358. doi: 10.1371/journal.pcbi.1006202.

[11] Katriona Shea, Michael J Tildesley, Michael C Runge, Christopher J Fonnesbeck, and Matthew J Ferrari. Adaptive Management and the Value of Information: Learning Via Intervention in Epidemiology. *PLoS Biology*, 12(10):9–12, 2014. ISSN 15457885. doi: 10.1371/journal.pbio.1001970.

[12] M J Keeling, M E J Woolhouse, D J Shaw, L Matthews, M Chase-Topping, D T Haydon, S J Cornell, J Kappey, J Wilesmith, and B T Grenfell. Dynamics of the 2001 UK foot and mouth epidemic: Stochastic dispersal in a heterogeneous landscape. *Science*, 294(5543):813–817, 2001. ISSN 00368075. doi: 10.1126/science.1065973.

[13] N. M. Ferguson, C. A. Donnelly, and R. M. Anderson. Transmission intensity and impact of control policies on the foot and mouth epidemic in Great Britain. *Nature*, 413(6855):542–548, 2001. ISSN 00280836. doi: 10.1038/35097116.

[14] W. J.M. Probert, S. Lakkur, C. J. Fonnesbeck, K. Shea, M. C. Runge, M. J. Tildesley, and M. J. Ferrari. Context matters: Using reinforcement learning to develop human-readable, state-dependent outbreak response policies. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 2019. ISSN 14712970. doi: 10.1098/rstb.2018.0277.

[15] Peter M. Dawson, Marleen Werkman, Ellen Brooks-Pollock, and Michael J. Tildesley. Epidemic predictions in an imperfect world: Modelling disease spread with partial data. *Proceedings of the Royal Society B: Biological Sciences*, 2015. ISSN 14712954. doi: 10.1098/rspb.2015.0205.

[16] Tom Lindström, Michael Tildesley, and Colleen Webb. A Bayesian Ensemble Approach for Epidemiological Projections. *PLoS Computational Biology*, 2015. ISSN 15537358. doi: 10.1371/journal.pcbi.1004187.

[17] Chris P. Jewell, Theodore Kypraios, Peter Neal, and Gareth O. Roberts. Bayesian analysis for emerging infectious diseases. *Bayesian Analysis*, 4(3):465–498, 2009. ISSN 19360975. doi: 10.1214/09-BA417.

[18] Steven Riley, Christophe Fraser, Christl A. Donnelly, Azra C. Ghani, Laith J. Abu-Raddad, Anthony J. Hedley, Gabriel M. Leung, Lai Ming Ho, Tai Hing Lam, Thuan Q. Thach, Patsy Chau, King Pan Chan, Su Vui Lo, Pak Yin Leung, Thomas Tsang, William Ho, Koon Hung Lee, Edith M.C. Lau, Neil M. Ferguson, and Roy M. Anderson. Transmission dynamics of the etiological agent of SARS in Hong Kong: Impact of public health interventions. *Science*, 2003. ISSN 00368075. doi: 10.1126/science.1086478.

[19] Alison Abbott and Helen Pearson. Fear of human pandemic grows as bird flu sweeps through Asia, 2004. ISSN 00280836.

[20] Christophe Fraser, Christl A. Donnelly, Simon Cauchemez, William P. Hanage, Maria D. Van Kerkhove, T. Déirdre Hollingsworth, Jamie Griffin, Rebecca F. Baggaley, Helen E. Jenkins, Emily J. Lyons, Thibaut Jombart, Wes R. Hinsley, Nicholas C. Grassly, Francois Balloux, Azra C. Ghani, Neil M. Ferguson, Andrew Rambaut, Oliver G. Pybus, Hugo Lopez-Gatell, Celia M. Alpuche-Aranda, Ietza Bojorquez Chapela, Ethel Palacios Zavala, Dulce Ma. Espejo Guevara, Francesco Checchi, Erika Garcia, Stephane Hugonnet, and Cathy Roth. Pandemic potential of a strain of influenza A (H1N1): Early findings. *Science*, 2009. ISSN 00368075. doi: 10.1126/science.1176062.

[21] Marc Lipsitch, Steven Riley, Simon Cauchemez, Azra C. Ghani, and Neil M. Ferguson. Managing and reducing uncertainty in an emerging influenza pandemic. *New England Journal of Medicine*, 2009. ISSN 15334406. doi: 10.1056/NEJMp0904380.

[22] Jimmy Boon Som Ong, Mark I.cheng Chen, Alex R. Cook, Huey Chyi Lee, Vernon J. Lee, Raymond Tzer Pin Lin, Paul Ananth Tambyah, and Lee Gan Goh. Real-time epidemic monitoring and forecasting of H1N1-2009 using influenza-like illness from general practice and family doctor clinics in singapore. *PLoS ONE*, 2010. ISSN 19326203. doi: 10.1371/journal.pone.0010036.

[23] Simon Cauchemez, Pierre Yves Boëlle, Guy Thomas, and Alain Jacques Valleron. Estimating in real time the efficacy of measures to control emerging communicable diseases. *American Journal of Epidemiology*, 2006. ISSN 00029262. doi: 10.1093/aje/kwj274.

[24] Simon Cauchemez, Pierre Yves Boëlle, Christl A. Donnelly, Neil M. Ferguson, Guy Thomas, Gabriel M. Leung, Anthony J. Hedley, Roy M. Anderson, and Alain Jacques Valleron. Real-time estimates in early detection of SARS. *Emerging Infectious Diseases*, 2006. ISSN 10806040. doi: 10.3201/eid1201.050593.

[25] Luís M.A. Bettencourt and Ruy M. Ribeiro. Real time bayesian estimation of the epidemic potential of emerging infectious diseases. *PLoS ONE*, 2008. ISSN 19326203. doi: 10.1371/journal.pone.0002185.

[26] Ian M. Hall, R. Gani, H. E. Hughes, and S. Leach. Real-time epidemic forecasting for pandemic influenza. *Epidemiology and Infection*, 2007. ISSN 09502688. doi: 10.1017/S0950268806007084.

[27] Marc Lipsitch, Frederick G. Hayden, Benjamin J. Cowling, and Gabriel M. Leung. How to maintain surveillance for novel influenza A H1N1 when there are too many cases to count, 2009. ISSN 01406736.

[28] Nilimesh Halder, Joel K. Kelso, and George J. Milne. Developing guidelines for school closure interventions to be used during a future influenza pandemic. *BMC Infectious Diseases*, 2010. ISSN 14712334. doi: 10.1186/1471-2334-10-221.

[29] Reza Yaesoubi and Ted Cohen. Identifying cost-effective dynamic policies to control epidemics. *Statistics in Medicine*, 2016. ISSN 10970258. doi: 10.1002/sim.7047.

[30] Jacco Wallinga, Michiel Van Bovena, and Marc Lipsitch. Optimizing infectious disease interventions during an emerging epidemic. *Proceedings of the National Academy of Sciences of the United States of America*, 2010. ISSN 00278424. doi: 10.1073/pnas.0908491107.

[31] Freya M. Shearer, Robert Moss, Jodie McVernon, Joshua V. Ross, and James M. McCaw. Infectious disease pandemic planning and response: Incorporating decision analysis, 2020. ISSN 15491676.

[32] Jean Paul Chretien, Steven Riley, and Dylan B. George. Mathematical modeling of the West Africa ebola epidemic. *eLife*, 2015. ISSN 2050084X. doi: 10.7554/eLife.09186.

[33] Anton Camacho, Adam Kucharski, Yvonne Aki-Sawyerr, Mark A. White, Stefan Flasche, Marc Baguelin, Timothy Pollington, Julia R. Carney, Rebecca Glover, Elizabeth Smout, Amanda Tiffany, W. John Edmunds, and Sebastian Funk. Temporal Changes in Ebola Transmission in Sierra Leone and Implications for Control Requirements: a Real-time Modelling Study. *PLoS Currents*, 2015. ISSN 2157-3999. doi: 10.1371/currents.outbreaks.406ae55e83ec0b5193e30856b9235ed2.

[34] Sebastian Funk, Anton Camacho, Adam J. Kucharski, Rosalind M. Eggo, and W. John Edmunds. Real-time forecasting of infectious disease dynamics with a stochastic semi-mechanistic model. *Epidemics*, 2018. ISSN 18780067. doi: 10.1016/j.epidem.2016.11.003.

[35] Pierre Nouvellet, Tini Garske, Harriet L. Mills, Gemma Nedjati-Gilani, Wes Hinsley, Isobel M. Blake, Maria D. Van Kerkhove, Anne Cori, Ilaria Dorigatti, Thibaut Jombart, Steven Riley, Christophe Fraser, Christl A. Donnelly, and Neil M. Ferguson. The role of rapid diagnostics in managing Ebola epidemics. *Nature*, 2015. ISSN 14764687. doi: 10.1038/nature16041.

[36] Gerardo Chowell, Cécile Viboud, Lone Simonsen, Stefano Merler, and Alessandro Vespignani. Perspectives on model forecasts of the 2014-2015 Ebola epidemic in West Africa: Lessons and the way forward. *BMC Medicine*, 2017. ISSN 17417015. doi: 10.1186/s12916-017-0811-y.

[37] Cécile Viboud, Kaiyuan Sun, Robert Gaffey, Marco Ajelli, Laura Fumanelli, Stefano Merler, Qian Zhang, Gerardo Chowell, Lone Simonsen, and Alessandro Vespignani. The RAPIDD ebola forecasting challenge: Synthesis and lessons learnt. *Epidemics*, 2018. ISSN 18780067. doi: 10.1016/j.epidem.2017.08.002.

[38] Adam J. Kucharski, Timothy W. Russell, Charlie Diamond, Yang Liu, John Edmunds, Sebastian Funk, Rosalind M. Eggo, Fiona Sun, Mark Jit, James D. Munday, Nicholas Davies, Amy Gimma, Kevin van Zandvoort, Hamish Gibbs, Joel Hellewell, Christopher I. Jarvis, Sam Clifford, Billy J. Quilty, Nikos I. Bosse, Sam Abbott, Petra Klepac, and Stefan Flasche. Early dynamics of transmission and control of COVID-19: a mathematical modelling study. *The Lancet Infectious Diseases*, 2020. ISSN 14744457. doi: 10.1016/S1473-3099(20)30144-4.

[39] Chaolong Wang, Li Liu, Xingjie Hao, Huan Guo, Qi Wang, Jiao Huang, Na He, Hongjie Yu, Xihong Lin, An Pan, Sheng Wei, and Tangchun Wu. Evolving Epidemiology and Impact of Non-pharmaceutical Interventions on the Outbreak of Coronavirus Disease 2019 in Wuhan, China. *medRxiv*, 2020. doi: 10.1101/2020.03.03.20030593.

[40] Kiesha Prem, Yang Liu, Timothy W. Russell, Adam J. Kucharski, Rosalind M. Eggo, Nicholas Davies, Stefan Flasche, Samuel Clifford, Carl A.B. Pearson, James D. Munday, Sam Abbott, Hamish Gibbs, Alicia Rosello, Billy J. Quilty, Thibaut Jombart, Fiona Sun, Charlie Diamond, Amy Gimma, Kevin van Zandvoort, Sebastian Funk, Christopher I. Jarvis, W. John Edmunds, Nikos I. Bosse, Joel Hellewell, Mark Jit, and Petra Klepac. The effect of control strategies to reduce social mixing on outcomes of the COVID-19 epidemic in Wuhan, China: a modelling study. *The Lancet Public Health*, 2020. ISSN 24682667. doi: 10.1016/S2468-2667(20)30073-6.

[41] World Health Organization. Novel Coronavirus (2019-nCoV) Situation Report - 105., 2020. URL `https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200504-covid-19-sitrep-105.pdf?sfvrsn=4cdda8af_2`.

[42] Craig R Allen, Joseph J Fontaine, Kevin L Pope, and Ahjond S Garmestani. Adaptive management for a turbulent future. *Journal of Environmental Management*, 92 (5):1339–1345, 2011. ISSN 03014797. doi: 10.1016/j.jenvman.2010.11.019. URL `http://dx.doi.org/10.1016/j.jenvman.2010.11.019`.

[43] C Walters. Adaptive Management of Renewable Resources. *Bulletin of Marine Science*, 41(3):374, 1986. URL `http://www.blackburnpress.com/admanofrenre.html`.

[44] C.S. Holling. Adaptive Environmental Assessment and Management. *International Series on Applied Systems Analysis*, page 402, 1978.

[45] Raymond J. H. Beverton and Sidney J. Holt. *On the Dynamics of Exploited Fish Populations*. 1993. doi: 10.1007/978-94-011-2106-4.

[46] C J Walters and R Hilborn. Ecological Optimization and Adaptive Management. *Annual Review of Ecology and Systematics*, 1978. ISSN 0066-4162. doi: 10.1146/annurev.es.09.110178.001105.

[47] Martin J Westgate, Gene E Likens, and David B Lindenmayer. Adaptive management of biological systems: A review. *Biological Conservation*, 158:128–139, 2013. ISSN 00063207. doi: 10.1016/j.biocon.2012.08.016. URL `http://dx.doi.org/10.1016/j.biocon.2012.08.016`.

[48] Jamie E. McFadden, Tim L. Hiller, and Andrew J. Tyre. Evaluating the efficacy of adaptive management approaches: Is there a formula for success? *Journal of Environmental Management*, 2011. ISSN 03014797. doi: 10.1016/j.jenvman.2010.10.038.

[49] Carl Walters, Josh Korman, Lawrence E. Stevens, and Barry Gold. Ecosystem modeling for evaluation of adaptive management policies in the Grand Canyon, 2000. ISSN 17083087.

[50] Byron K. Williams and James D. Nichols. Systems identification and the adaptive management of waterfowl in the United States. *Wildlife Biology*, 2001. ISSN 0909-6396. doi: 10.2981/wlb.2001.027.

[51] Daniel Merl, Leah R. Johnson, Robert B. Gramacy, and Marc Mangel. A statistical framework for the adaptive management of epidemiological interventions. *PLoS ONE*, 2009. ISSN 19326203. doi: 10.1371/journal.pone.0005807.

[52] Byron K. Williams, Mitchell J. Eaton, and David R. Breininger. Adaptive resource management and the value of information. *Ecological Modelling*, 2011. ISSN 03043800. doi: 10.1016/j.ecolmodel.2011.07.003.

[53] H. P Possingham, S. J Andelman, B. R Noon, Stephen C. Trombulak, and H. R Pulliam. Making Smart Conservation Decisions. In *Research priorities for nature conservation*. 2000.

[54] Byron K. Williams and Eleanor D. Brown. Adaptive management: The U.S. department of the interior applications guide. In *Adaptive Management of Natural Resources: Concepts and Applications*. 2014. ISBN 9781633213722.

[55] Carl Walters. Challenges in adaptive management of riparian and coastal ecosystems. *Ecology and Society*, 1997. ISSN 17083087. doi: 10.5751/es-00026-010201.

[56] Shou-Li Li, Ottar N. Bjørnstad, Matthew J. Ferrari, Riley Mummah, Michael C. Runge, Christopher J. Fonnesbeck, Michael J. Tildesley, William J. M. Probert, and Katriona Shea. Essential information: Uncertainty and optimal control of Ebola outbreaks. *Proceedings of the National Academy of Sciences*, 2017. ISSN 0027-8424. doi: 10.1073/pnas.1617482114.

[57] William J.M. Probert, Cindy E. Hauser, Eve McDonald-Madden, Michael C. Runge, Peter W.J. Baxter, and Hugh P. Possingham. Managing and learning with multiple models: Objectives and optimization algorithms. *Biological Conservation*, 2011. ISSN 00063207. doi: 10.1016/j.biocon.2010.07.031.

[58] Byron K. Williams. Passive and active adaptive management: Approaches and an example. *Journal of Environmental Management*, 2011. ISSN 03014797. doi: 10.1016/j.jenvman.2010.10.039.

[59] Michael C. Runge. Active adaptive management for reintroduction of an animal population. *Journal of Wildlife Management*, 2013. ISSN 0022541X. doi: 10.1002/jwmg.571.

[60] Michael A. McCarthy and Hugh P. Possingham. Active adaptive management for conservation. *Conservation Biology*, 2007. ISSN 08888892. doi: 10.1111/j.1523-1739.2007.00677.x.

[61] Richard Bellman. A Markovian Decision Process. *Indiana University Mathematics Journal*, 1957. ISSN 0022-2518. doi: 10.1512/iumj.1957.6.56038.

[62] Martin L. Puterman. Markov decision processes, 1990. ISSN 09270507.

[63] Anthony R. Cassandra, Leslie Pack Kaelbling, and Michael L. Littman. Acting optimally in partially observable stochastic domains. In *Proceedings of the National Conference on Artificial Intelligence*, 1994.

[64] Leslie Pack Kaelbling, Michael L. Littman, and Anthony R. Cassandra. Planning and acting in partially observable stochastic domains. *Artificial Intelligence*, 1998. ISSN 00043702. doi: 10.1016/s0004-3702(98)00023-x.

[65] Matthijs T.J. Spaan. Partially observable markov decision processes. In *Adaptation, Learning, and Optimization*. 2012. doi: 10.1007/978-3-642-27645-3_12.

[66] Byron K. Williams. Adaptive management of natural resources-framework and issues. *Journal of Environmental Management*, 2011. ISSN 03014797. doi: 10.1016/j.jenvman.2010.10.041.

[67] R. Gregory, D. Ohlson, and J. Arvai. Deconstructing adaptive management: Criteria for applications to environmental management. *Ecological Applications*, 2006. ISSN 10510761. doi: 10.1890/1051-0761(2006)016[2411:DAMCFA]2.0.CO;2.

[68] Joseph J. Fontaine. Improving our legacy: Incorporation of adaptive management into state wildlife action plans. *Journal of Environmental Management*, 2011. ISSN 03014797. doi: 10.1016/j.jenvman.2010.10.015.

[69] L. H. Gunderson. Ecological resilience - In theory and application. *Annual Review of Ecology and Systematics*, 2000. ISSN 00664162. doi: 10.1146/annurev.ecolsys.31.1.425.

[70] C. Walters, L. Gunderson, and C. S. Holling. Experimental policies for water management in the Everglades. *Ecological Applications*, 1992. ISSN 10510761. doi: 10.2307/1941775.

[71] J. Walter Milon, Clyde F. Kiker, and Donna J. Lee. Ecosystem Management and the Florida Everglades: The Role of Social Scientists. *Journal of Agricultural and Applied Economics*, 1997. ISSN 1074-0708. doi: 10.1017/s1074070800007586.

[72] Lance Gunderson and Stephen S. Light. Adaptive management and adaptive governance in the everglades ecosystem. *Policy Sciences*, 2006. ISSN 00322687. doi: 10.1007/s11077-006-9027-2.

[73] C. J. Walters and C. S. Holling. Large-scale management experiments and learning by doing. *Ecology*, 1990. ISSN 00129658. doi: 10.2307/1938620.

[74] Kai N. Lee. Appraising adaptive management, 1999. ISSN 17083087.

[75] Vicky J. Meretsky, David L. Wegner, and Lawrence E. Stevens. Balancing endangered species and ecosystems: A case study of adaptive management in Grand Canyon. *Environmental Management*, 2000. ISSN 0364152X. doi: 10.1007/s002670010045.

[76] Roger S. Pulwarty and Theodore S. Melis. Climate extremes and adaptive management on the Colorado River: Lessons from the 1997-1998 ENSO event. *Journal of Environmental Management*, 2001. ISSN 03014797. doi: 10.1006/jema.2001.0494.

[77] Fred A. Johnson, William L. Kendall, and James A. Dubovsky. Conditions and limitations on learning in the adaptive management of mallard harvests. *Wildlife Society Bulletin*, 2002. ISSN 0091-7648.

[78] Byron K. Williams, Fred A. Johnson, and Khristi Wilkins. Uncertainty and the Adaptive Management of Waterfowl Harvests. *The Journal of Wildlife Management*, 1996. ISSN 0022541X. doi: 10.2307/3802220.

[79] James D. Nichols, Michael C. Runge, Fred A. Johnson, and Byron K. Williams. Adaptive harvest management of North American waterfowl populations: A brief history and future prospects, 2007. ISSN 00218375.

[80] Conor P. McGowan, David R. Smith, John A. Sweka, Julien Martin, James D. Nichols, Richard Wong, James E. Lyons, Lawrence J. Niles, Kevin Kalasz, Jeffrey Brust, Michelle Klopfer, and Braddock Spear. Multispecies modeling for adaptive management of horseshoe crabs and red knots in the delaware bay. *Natural Resource Modeling*, 2011. ISSN 08908575. doi: 10.1111/j.1939-7445.2010.00085.x.

[81] Michael J. Conroy, Richard J. Barker, Peter W. Dillingham, David Fletcher, Andrew M. Gormley, and Ian M. Westbrooke. Application of decision theory to conservation management: Recovery of Hector's dolphin. *Wildlife Research*, 2008. ISSN 10353712. doi: 10.1071/WR07147.

[82] Carl J. Walters. Is adaptive management helping to solve fisheries problems?, 2007. ISSN 00447447.

[83] Steven J.D. Martell and Carl J. Walters. Experimental policies for rebuilding depleted stocks. *Canadian Journal of Fisheries and Aquatic Sciences*, 2008. ISSN 0706652X. doi: 10.1139/F08-061.

[84] Wyatt F. Cross, Colden V. Baxter, Kevin C. Donner, Emma J. Rosi-Marshall, Theodore A. Kennedy, Robert O. Hall, Holly A. Wellard Kelly, and R. Scott Rogers. Ecosystem ecology meets adaptive management: Food web response to a controlled flood on the Colorado River, Glen Canyon. *Ecological Applications*, 2011. ISSN 10510761. doi: 10.1890/10-1719.1.

[85] Terence P. Hughes, Lance H. Gunderson, Carl Folke, Andrew H. Baird, David Bellwood, Fikret Berkes, Beatrice Crona, Ariella Helfgott, Heather Leslie, Jon Norberg, Magnus Nyström, Per Olsson, Henrik Österblom, Marten Scheffer, Heidi Schuttenberg, Robert S.

Steneck, Maria Tengö, Max Troell, Brian Walker, James Wilson, and Boris Worm. Adaptive management of the great barrier reef and the grand canyon world heritage areas, 2007. ISSN 00447447.

[86] Robert D Hayes, Richard Farnell, Richard M P Ward, Jean Carey, Michael Dehn, Gerald W Kuzyk, Alan M Baer, Craig L Gardner, and Mark O'Donoghue. Experimental Reduction of Wolves in the Yukon: Ungulate Responses and Management Implications. *Wildlife Monographs*, 2003. ISSN 00840173, 19385455.

[87] Koichi Kaji, Takashi Saitoh, Hiroyuki Uno, Hiroyuki Matsuda, and Kohji Yamamura. Adaptive management of sika deer populations in Hokkaido, Japan: Theory and practice, 2010. ISSN 14383896.

[88] A. Marm Kilpatrick, Colin M. Gillin, and Peter Daszak. Wildlife-livestock conflict: The risk of pathogen transmission from bison to cattle outside Yellowstone National Park. *Journal of Applied Ecology*, 2009. ISSN 00218901. doi: 10.1111/j.1365-2664.2008.01602.x.

[89] Nathan Varley and Mark S. Boyce. Adaptive management for reintroductions: Updating a wolf recovery model for Yellowstone National Park. *Ecological Modelling*, 2006. ISSN 03043800. doi: 10.1016/j.ecolmodel.2005.09.001.

[90] Doug P. Armstrong, Isabel Castro, and Richard Griffiths. Using adaptive management to determine requirements of re-introduced populations: The case of the New Zealand hihi. *Journal of Applied Ecology*, 2007. ISSN 00218901. doi: 10.1111/j.1365-2664.2007.01320.x.

[91] John Innes, Rod Hay, Ian Flux, Philip Bradfield, Hazel Speed, and Paul Jansen. Successful recovery of North Island kokako Callaeas cinerea wilsoni populations, by adaptive management. *Biological Conservation*, 1999. ISSN 00063207. doi: 10.1016/S0006-3207(98)00053-6.

[92] Felipe Cruz, Victor Carrion, Karl J. Campbell, Christian Lavoie, and C. Josh Donlan. Bio-Economics of Large-Scale Eradication of Feral Goats From Santiago Island, Galápagos. *Journal of Wildlife Management*, 2009. ISSN 0022-541X. doi: 10.2193/2007-551.

[93] PAUL B. CONN and WILLIAM L. KENDALL. EVALUATING MALLARD ADAPTIVE MANAGEMENT MODELS WITH TIME SERIES. *Journal of Wildlife Management*, 2004. ISSN 0022-541X. doi: 10.2193/0022-541x(2004)068[1065:emammw]2.0.co;2.

[94] James E. Lyons, Michael C. Runge, Harold P. Laskowski, and William L. Kendall. Monitoring in the Context of Structured Decision-Making and Adaptive Management. *Journal of Wildlife Management*, 2008. ISSN 0022-541X. doi: 10.2193/2008-141.

[95] Bernard T. Bormann, Richard W. Haynes, and Jon R. Martin. Adaptive Management of Forest Ecosystems: Did Some Rubber Hit the Road? *BioScience*, 2007. ISSN 0006-3568. doi: 10.1641/b570213.

[96] Andrew N. Gray. Adaptive ecosystem management in the Pacific Northwest: A case study from Coastal Oregon. *Ecology and Society*, 2000. ISSN 17083087. doi: 10.5751/es-00224-040206.

[97] C. A. McAlpine, T. A. Spies, P. Norman, and A. Peterson. Conserving forest biodiversity across multiple land ownerships: Lessons from the Northwest Forest Plan and the Southeast Queensland regional forests agreement (Australia). *Biological Conservation*, 2007. ISSN 00063207. doi: 10.1016/j.biocon.2006.09.009.

[98] Randy Molina, Bruce G. Marcot, and Robin Lesher. Protecting rare, old-growth, forest-associated species under the survey and manage program guidelines of the Northwest Forest Plan, 2006. ISSN 08888892.

[99] George H. Stankey, Bernard T. Bormann, Clare Ryan, Bruce Shindler, Victoria Sturtevant, Roger N. Clark, and Charles Philpot. Adaptive management and the northwest forest plan rhetoric and reality. *Journal of Forestry*, 2003. ISSN 0022-1201. doi: 10.1093/jof/101.1.40.

[100] Alison L. Howes, Martine Maron, and Clive A. Mcalpine. Bayesian networks and adaptive management of wildlife habitat. *Conservation Biology*, 2010. ISSN 08888892. doi: 10.1111/j.1523-1739.2010.01451.x.

[101] Jason Cummings, Nick Reid, Ian Davies, and Carl Grant. Adaptive restoration of sand-mined areas for biological conservation. *Journal of Applied Ecology*, 2005. ISSN 00218901. doi: 10.1111/j.1365-2664.2005.01003.x.

[102] Allan J. Perkins, Hywel E. Maggs, Adam Watson, and Jeremy D. Wilson. Adaptive management and targeting of agri-environment schemes does benefit biodiversity: A case study of the corn bunting Emberiza calandra. *Journal of Applied Ecology*, 2011. ISSN 00218901. doi: 10.1111/j.1365-2664.2011.01958.x.

[103] Naomi V. Bradbury, William J.M. Probert, Katriona Shea, Michael C. Runge, Christopher J. Fonnesbeck, Matt J. Keeling, Matthew J. Ferrari, and Michael J. Tildesley. Quantifying the Value of Perfect Information in Emergency Vaccination Campaigns. *PLoS Computational Biology*, 13(2), 2017. ISSN 15537358. doi: 10.1371/journal.pcbi.1005318.

[104] Robin N. Thompson, Christopher A. Gilligan, and Nik J. Cunniffe. Control fast or control smart: When should invading pathogens be controlled? *PLoS Computational Biology*, 2018. ISSN 15537358. doi: 10.1371/journal.pcbi.1006014.

[105] Nik J. Cunniffe, Richard O.J.H. Stutt, R. Erik DeSimone, Tim R. Gottwald, and Christopher A. Gilligan. Optimising and Communicating Options for the Control of Invasive Plant Disease When There Is Epidemiological Uncertainty. *PLoS Computational Biology*, 2015. ISSN 15537358. doi: 10.1371/journal.pcbi.1004211.

[106] Nik J. Cunniffe, Richard C. Cobb, Ross K. Meentemeyer, David M. Rizzo, and Christopher A. Gilligan. Modeling when, where, and how to manage a forest epidemic,

motivated by sudden oak death in California. *Proceedings of the National Academy of Sciences of the United States of America*, 2016. ISSN 10916490. doi: 10.1073/pnas.1602153113.

[107] Shou Li Li, Matthew J. Ferrari, Ottar N. Bjørnstad, Michael C. Runge, Christopher J. Fonnesbeck, Michael J. Tildesley, David Pannell, and Katriona Shea. Concurrent assessment of epidemiological and operational uncertainties for optimal outbreak control: Ebola as a case study. *Proceedings of the Royal Society B: Biological Sciences*, 2019. ISSN 14712954. doi: 10.1098/rspb.2019.0774.

[108] Michael Ludkovski and Jarad Niemi. Optimal Dynamic Policies for Influenza Management. *Statistical Communications in Infectious Diseases*, 2010. ISSN 1948-4690. doi: 10.2202/1948-4690.1020.

[109] E. H. Bussell, C. E. Dangerfield, C. A. Gilligan, and N. J. Cunniffe. Applying optimal control theory to complex epidemiological models to inform real-world disease management. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 2019. ISSN 14712970. doi: 10.1098/rstb.2018.0284.

[110] M. Stone, H. Raiffa, and R. Schlaifer. Applied Statistical Decision Theory. *Technometrics*, 1961. ISSN 00401706. doi: 10.2307/1266736.

[111] Ronald A. Howard. Information Value Theory. *IEEE Transactions on Systems Science and Cybernetics*, 1966. ISSN 21682887. doi: 10.1109/TSSC.1966.300074.

[112] Ronald A. Howard. Value of Information Lotteries. *IEEE Transactions on Systems Science and Cybernetics*, 1967. ISSN 21682887. doi: 10.1109/TSSC.1967.300108.

[113] Ronald A. Howard. The Foundations of Decision Analysis. *IEEE Transactions on Systems Science and Cybernetics*, 1968. ISSN 21682887. doi: 10.1109/TSSC.1968.300115.

[114] Kimberly M. Thompson and John D. Graham. Going beyond the single number: Using probabilistic risk assessment to improve risk management. *Human and Ecological Risk Assessment (HERA)*, 1996. ISSN 10807039. doi: 10.1080/10807039609383660.

[115] James C. Felli and Gordon B. Hazen. Sensitivity analysis and the expected value of perfect information. *Medical Decision Making*, 1998. ISSN 0272989X. doi: 10.1177/0272989X9801800117.

[116] James C. Felli and Gordon B. Hazen. A Bayesian approach to sensitivity analysis. *Health Economics*, 1999. ISSN 10579230. doi: 10.1002/(SICI)1099-1050(199905)8:3⟨263::AID-HEC426⟩3.0.CO;2-S.

[117] Fumie Yokota and Kimberly M. Thompson. Value of information literature analysis: A review of applications in health risk management, 2004. ISSN 0272989X.

[118] K. Claxton. Bayesian approaches to the value of information: Implications for the regulation of new pharmaceuticals. *Health Economics*, 1999. ISSN 10579230. doi: 10.1002/(SICI)1099-1050(199905)8:3⟨269::AID-HEC425⟩3.0.CO;2-D.

[119] K. Claxton and K. M. Thompson. A dynamic programming approach to the efficient design of clinical trials. *Journal of Health Economics*, 2001. ISSN 01676296. doi: 10.1016/S0167-6296(01)00093-5.

[120] Karl Claxton, Peter J. Neumann, Sally Araki, and Milton C. Weinstein. Bayesian value-of-information analysis: An application to a policy model of Alzheimer's disease, 2001. ISSN 02664623.

[121] Adam M. Finkel and John S. Evans. Evaluating the benefits of uncertainty reduction in environmental health risk management. *Journal of the Air Pollution Control Association*, 1987. ISSN 08940630. doi: 10.1080/08940630.1987.10466310.

[122] Janet M. Wagner, Uri Shamir, and Hamid R. Nemati. Groundwater quality management under uncertainty: stochastic programming approaches and the value of information. *Water Resources Research*, 1992. ISSN 19447973. doi: 10.1029/92WR00038.

[123] Sean L. Maxwell, Jonathan R. Rhodes, Michael C. Runge, Hugh P. Possingham, Chooi Fei Ng, and Eve Mcdonald-Madden. How much is new information worth? Evaluating the financial benefit of resolving management uncertainty. *Journal of Applied Ecology*, 2015. ISSN 13652664. doi: 10.1111/1365-2664.12373.

[124] Michael C. Runge, Sarah J. Converse, and James E. Lyons. Which uncertainty? Using expert elicitation and expected value of information to design an adaptive program. *Biological Conservation*, 2011. ISSN 00063207. doi: 10.1016/j.biocon.2010.12.020.

[125] Byron K Williams, Mitchell J Eaton, and David R Breininger. Adaptive resource management and the value of information. *Ecological Modelling*, 222(18):3429–3436, 2011. ISSN 03043800. doi: 10.1016/j.ecolmodel.2011.07.003. URL `http://dx.doi.org/10.1016/j.ecolmodel.2011.07.003`.

[126] Shou Li Li, Ottar N. Bjørnstad, Matthew J. Ferrari, Riley Mummah, Michael C. Runge, Christopher J. Fonnesbeck, Michael J. Tildesley, William J.M. Probert, and Katriona Shea. Essential information: Uncertainty and optimal control of Ebola outbreaks. *Proceedings of the National Academy of Sciences of the United States of America*, 2017. ISSN 10916490. doi: 10.1073/pnas.1617482114.

[127] Naomi V. Bradbury, William J.M. Probert, Katriona Shea, Michael C. Runge, Christopher J. Fonnesbeck, Matt J. Keeling, Matthew J. Ferrari, and Michael J. Tildesley. Quantifying the Value of Perfect Information in Emergency Vaccination Campaigns. *PLoS Computational Biology*, 2017. ISSN 15537358. doi: 10.1371/journal.pcbi.1005318.

[128] Gavin J. Gibson. Markov chain Monte Carlo methods for fitting spatiotemporal stochastic models in plant epidemiology. *Journal of the Royal Statistical Society. Series C: Applied Statistics*, 1997. ISSN 00359254. doi: 10.1111/1467-9876.00061.

[129] Gavin J. Gibson and Eric Renshaw. Estimating parameters in stochastic compartmental models using Markov chain methods. *IMA Journal of Mathemathics Applied in Medicine and Biology*, 1998. ISSN 02650746. doi: 10.1093/imammb15.1.19.

[130] Philip D. O'Neill and Gareth O. Roberts. Bayesian inference for partially observed stochastic epidemics. *Journal of the Royal Statistical Society. Series A: Statistics in Society*, 1999. ISSN 09641998. doi: 10.1111/1467-985X.00125.

[131] Philip D. O'Neill. A tutorial introduction to Bayesian inference for stochastic epidemic models using Markov chain Monte Carlo methods. *Mathematical Biosciences*, 2002. ISSN 00255564. doi: 10.1016/S0025-5564(02)00109-8.

[132] Peter J. Neal and Gareth O. Roberts. Statistical inference and model selection for the 1861 Hagelloch measles epidemic. *Biostatistics*, 2004. ISSN 14654644. doi: 10.1093/biostatistics/5.2.249.

[133] George Streftaris and Gavin J. Gibson. Bayesian inference for stochastic epidemics in closed populations. *Statistical Modeling*, 2004. ISSN 1471082X. doi: 10.1191/1471082X04st065oa.

[134] Simon Duane, A. D. Kennedy, Brian J. Pendleton, and Duncan Roweth. Hybrid Monte Carlo. *Physics Letters B*, 1987. ISSN 03702693. doi: 10.1016/0370-2693(87)91197-X.

[135] Stan Development Team. Stan Modeling Language Users Guide and Reference Manual, Version 2.18.0., 2018. URL `http://mc-stan.org`.

[136] Matthew D. Hoffman and Andrew Gelman. The no-U-turn sampler: Adaptively setting path lengths in Hamiltonian Monte Carlo. *Journal of Machine Learning Research*, 2014. ISSN 15337928.

[137] Alana L. Moore and Michael A. Mccarthy. On valuing information in adaptive-management models. *Conservation Biology*, 2010. ISSN 08888892. doi: 10.1111/j.1523-1739.2009.01443.x.

[138] Alison P. Galvani, Martial L. Ndeffo-Mbah, Natasha Wenzel, and James E. Childs. Ebola vaccination: If not now, when?, 2014. ISSN 15393704.

[139] Alana L. Moore, Leila Walker, Michael C. Runge, Eve McDonald-Madden, and Michael A. McCarthy. Two-step adaptive management for choosing between two management actions. *Ecological Applications*, 2017. ISSN 19395582. doi: 10.1002/eap.1515.

[140] William J.M. Probert, Cindy E. Hauser, Eve McDonald-Madden, Michael C. Runge, Peter W.J. Baxter, and Hugh P. Possingham. Managing and learning with multiple models: Objectives and optimization algorithms. *Biological Conservation*, 144(4): 1237–1245, 2011. ISSN 00063207. doi: 10.1016/j.biocon.2010.07.031. URL `http://dx.doi.org/10.1016/j.biocon.2010.07.031`.

[141] Tiffany L. Bogich, Andrew M. Liebhold, and Katriona Shea. To sample or eradicate? A cost minimization model for monitoring and managing an invasive species. *Journal of Applied Ecology*, 2008. ISSN 00218901. doi: 10.1111/j.1365-2664.2008.01494.x.

[142] Peter W.J. Baxter and Hugh P. Possingham. Optimizing search strategies for invasive pests: Learn before you leap. *Journal of Applied Ecology*, 2011. ISSN 00218901. doi: 10.1111/j.1365-2664.2010.01893.x.

[143] Hedley S. Grantham, Kerrie A. Wilson, Atte Moilanen, Tony Rebelo, and Hugh P. Possingham. Delaying conservation actions for improved knowledge: How long should we wait? *Ecology Letters*, 2009. ISSN 1461023X. doi: 10.1111/j.1461-0248.2009.01287.x.

[144] Sebastian Funk, Iza Ciglenecki, Amanda Tiffany, Etienne Gignoux, Anton Camacho, Rosalind M. Eggo, Adam J. Kucharski, W. John Edmunds, Josephus Bolongei, Phillip Azuma, Peter Clement, Tamba S. Alpha, Esther Sterk, Barbara Telfer, Gregory Engel, Lucy Anne Parker, Motoi Suzuki, Nico Heijenberg, and Bruce Reeder. The impact of control strategies and behavioural changes on the elimination of ebola from lofa county, Liberia. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 2017. ISSN 14712970. doi: 10.1098/rstb.2016.0302.

[145] M. E. Halloran, C. J. Struchiner, and I. M. Longini. Study Designs for Evaluating Different Efficacy and Effectiveness Aspects of Vaccines. *American Journal of Epidemiology*, 1997. ISSN 0002-9262. doi: 10.1093/oxfordjournals.aje.a009196.

[146] World Health Organization. Ebola virus disease – Democratic Republic of the Congo Disease outbreak news: Update 30 May 2019, 2020. URL `https://www.who.int/csr/don/30-may-2019-ebola-drc/en/`.

[147] Alexis. Robert, Anton. Camacho, John W. Edmunds, Marc. Baguelin, Jean-Jacques Muyembe. Tamfum, Alicia. Rosello, Sakoba. Keita, and Rosalind M. Eggo. Effect of vaccinating health care workers to control Ebola virus disease: a modelling analysis of outbreak data. *bioRxiv*, 2017. doi: https://doi.org/10.1101/113506.

[148] World Health Organization. Ebola Virus Disease Democratic Republic of Congo External Situation Report 78., 2020. URL `https://www.who.int/publications/i/item/ebola-virus-disease-democratic-republic-of-congo-external-situation-report-78-2019`.

[149] WHO. Guidelines on clinical evaluation of vaccines: regulatory expectations. *WHO Technical Report*, 2004.

[150] W. A. Orenstein, R. H. Bernier, T. J. Dondero, A. R. Hinman, J. S. Marks, K. J. Bart, and B. Sirotkin. Field evaluation of vaccine efficacy. *Bulletin of the World Health Organization*, 1985. ISSN 00429686.

[151] Anton Camacho, Rosalind M. Eggo, Sebastian Funk, Conall H. Watson, Adam J. Kucharski, and W. John Edmunds. Estimating the probability of demonstrating

vaccine efficacy in the declining Ebola epidemic: A Bayesian modelling approach. *BMJ Open*, 2015. ISSN 20446055. doi: 10.1136/bmjopen-2015-009346.

[152] Benjamin J. Cowling, Irene O.L. Wong, Lai Ming Ho, Steven Riley, and Gabriel M. Leung. Methods for monitoring influenza surveillance data. *International Journal of Epidemiology*, 2006. ISSN 03005771. doi: 10.1093/ije/dyl162.

[153] Martial L. Ndeffo Mbah and Christopher A. Gilligan. Balancing detection and eradication for control of epidemics: Sudden oak death in mixed-species stands. *PLoS ONE*, 2010. ISSN 19326203. doi: 10.1371/journal.pone.0012317.

[154] Evan L. Ray and Nicholas G. Reich. Prediction of infectious disease epidemics via weighted density ensembles. *PLoS Computational Biology*, 2018. ISSN 15537358. doi: 10.1371/journal.pcbi.1005910.

[155] Martin Péron, Kai Helge Becker, Peter Bartlett, and Iadine Chadès. Fast-tracking stationary MOMDPs for adaptive management problems. In *31st AAAI Conference on Artificial Intelligence, AAAI 2017*, 2017.

[156] Ying Qi Zhao, Donglin Zeng, Eric B. Laber, and Michael R. Kosorok. New Statistical Learning Methods for Estimating Optimal Dynamic Treatment Regimes. *Journal of the American Statistical Association*, 2015. ISSN 1537274X. doi: 10.1080/01621459.2014.937488.